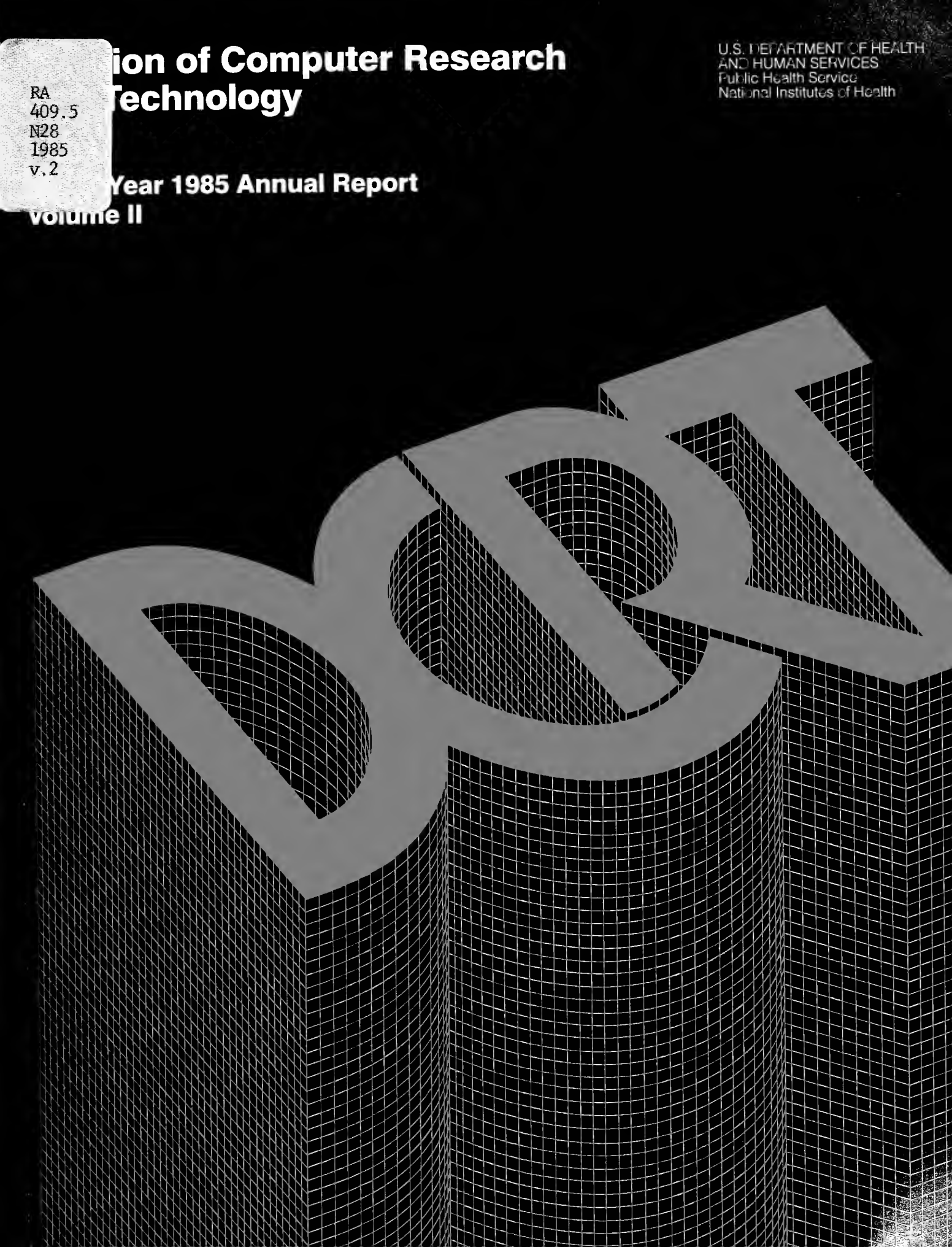
...ion of Computer Research ...Technology

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

...Year 1985 Annual Report
Volume II



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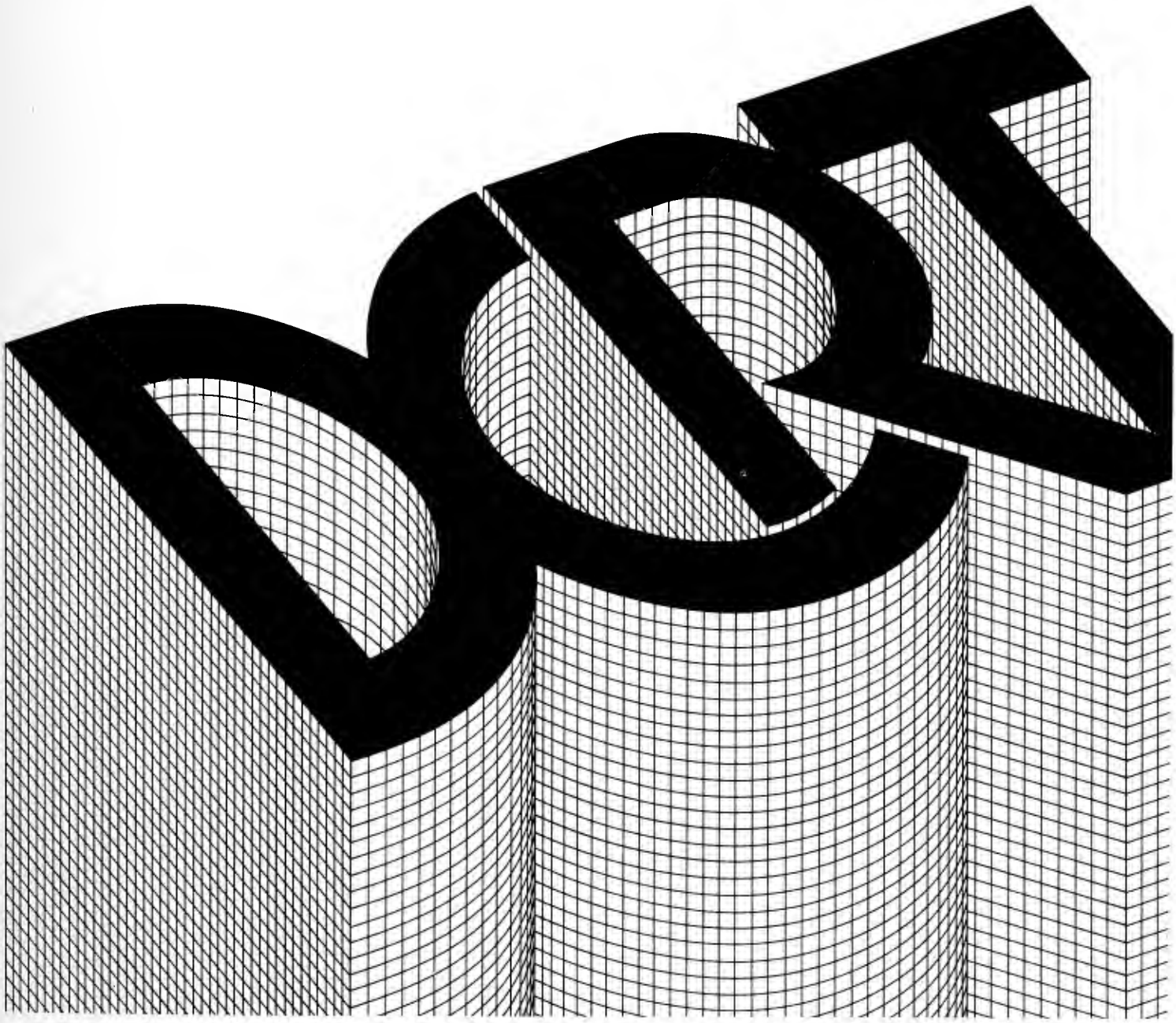

Foreword

The Division of Computer Research and Technology has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH. DCRT serves as a scientific and technological resource for other parts of PHS, and for other Federal organizations with biomedical and statistical computing needs.

DCRT programs focus on three primary activities: conducting research, developing computer systems, and providing computer facilities.

The *DCRT Fiscal Year 1985 Annual Report* describes our work in two volumes:

Volume 1 gives an overview of the work of each group, highlighting the year's accomplishments;
Volume 2 gives details about the projects and activities of each group.

Contents

Physical Sciences Laboratory

George H. Weiss, Chief

Summary of Activities

Biophysical Analysis. Studies were continued on theoretical models for the structure and dynamics of dense macromolecular systems. Simulation studies were performed to determine the fractional dimensionality and diffusion exponents that characterize materials with a fractal structure. A related investigation was made of the escape of drug molecules from the surfaces of encapsulated polymer matrices as a study of the kinetics of drug delivery systems. Small angle neutron scattering studies of biologically interesting materials have been initiated to determine interactions and structural ordering between macromolecules in dense solutions.

Correlation Function Spectroscopy/Laser Light Scattering. Methods have been developed for the analysis and interpretation of dynamic light scattering measurements of the gelation and elasticity of polymer lattices. These methods are presently being used to study biological gels exemplified by fibrin clots and cytoplasmic networks.

Solvent Effects on Macromolecules. A phenomenological statistical mechanical theory is being developed for calculating thermodynamic properties of proteins especially as they are affected by the solvent. Approximate techniques for deriving correlation functions presently are being tested.

Apollo System Development. This collaborative study with Richard Feldmann, DCRT/OD, has aimed at the completion of a molecular graphics facility available for use by NIH scientists. Work on the hardware for this system is almost complete as well as a scheme for predicting secondary structure of proteins. Further work will involve a combination of software development as well as the development of mathematical techniques to derive information of chemical interest using the software. Additional work will involve the study of tertiary structure and the integration of such results into presently available programs.

Instrumental Analysis. Work has continued on the optimization of NMR experiments to minimize the results of instrumental noise in the estimation of spin-lattice relaxation times. We have extended and applied exact Fourier representations of crystallographic probability densities to several direct methods for phase determination. Numerical methods have been devised for determining parameters that characterize dielectric properties of polymers. For their development it was necessary to generate accurate tables of stable law distributions. These will be useful to statisticians and scientists in other disciplines.

Studies in Mathematics and Statistics. Further work is in progress on the theory of diffusion on disordered structures such as fractal materials. A meeting was held on models for reaction rates in chemical physics.

Molecular Forces in Cellular Assembly. A joint theoretical and experimental investigation has been mounted on the combination of long-range and mechanical forces on the interaction of large molecules and membranes. Measurements have been made of forces between DNA double helices, suggesting that so-called hydrophobic forces can be explained in terms of the restructuring of water solvent between molecules.

Membrane Fusion. This year has seen a continuation of experiments to determine the physical factors that influence membrane fusion. These experiments are consistent with the idea that osmotic pressure plays a major role in the phenomenon.

Membrane Transport. Further experiments have been performed on the effects of various chemical and physical influences on the internal volume change during the opening and closing of ionic transmembrane channels. The observed changes are much larger than suggested by earlier theoretical ideas.

Consulting Services. A study is being made on the temporal pattern of the occurrence of post-traumatic epilepsy of head injured Vietnam veterans. Statistical analysis suggests that there are at least two populations, those who tend to have fits within a year or two after injury, and those who tend to have them on an average of about five years post-injury.

Personal Workstation Word Processing. Two word processing packages for the PC, DisplayWrite 2 and Multimate, were supported by DCRT. In addition to the

evaluation of different packages, we have consulted with others at NIH on the choice and use of word processing packages.

Computerized Typesetting of Scientific Papers. Programs developed for mainframe computers have been adapted for use on the PC-XT. This project is now complete.

Research Projects

Biophysical Analysis

Principal Investigator: Ralph J. Nossal, Ph.D. (DCRT/PSL). *Also:* S. Havlin, G. H. Weiss (DCRT/PSL); B. Trus (DCRT/CSL); S. H. Chen (Dept. Nucl. Engr./MIT); C. Glinka (Reactor Div./NBS); A. Bunde, H. E. Stanley (Physics Dept./Boston University).

This project comprises several investigations. Recent emphasis has been on studies of the structure and dynamics of dense macromolecular systems. For example, theoretical models have been used to study the geometrical and topological characteristics of disordered or irregular media such as gels and branched polymers. Analytical methods and Monte Carlo simulations have been developed to study the fractal dimensionality, conductivity, and diffusion exponents of those models. In a related activity, computer simulations of the escape of drug molecules from the surface pores of encapsulated polymer matrices have been performed and analyzed. Relationships have been determined for the rate of release as a function of the dimensionality and size of the matrix and uncoated surfaces.

Small angle neutron scattering (SANS) studies have been performed, in collaboration with scientists at the National Bureau of Standards and the Massachusetts Institute of Technology, to determine interactions and structural ordering between macromolecules in dense solutions of biopolymers. Computer-based procedures for deducing intermolecular forces from experimentally determined structure factors have been developed. The variation of macromolecular surface charge occurring when solution properties are changed has been investigated in samples containing as much as 20 percent wt/vol protein.

Publications:

Havlin, S., Nossal, R., Trus, B., and Weiss, G. H.: Diffusion on tree-like structures. *Phys. Rev.* 31: 7497-7499, 1985.

Havlin, S., Nossal, R., Trus, B., and Weiss, G. H.: Universal substructures of percolation clusters. *J. Phys.* A17: L957-960, 1984.

Correlation Function Spectroscopy/Laser Light Scattering

Principal Investigator: Ralph J. Nossal, Ph.D. (DCRT/PSL). *Also:* R. Bonner, Ph.D. (DRS/BEIB); D. E. Gaasterland, M.D. (NEI/Clinical Branch); N. Gershfeld (NIADDK/LBP); M. Litt, Ph.D. (Dept. Biomed. Eng./Univ. Pennsylvania).

Various studies utilizing laser light scattering have been undertaken, some in direct support of biomedical research being performed at NIH and similar institutions, others as part of a long-term technical development program. Recent emphasis has been on developing methods to probe phase transitions in lipid-water systems and on developing theories for interpreting measurements made with laser-Doppler blood flow instrumentation.

Instrumentation was developed to probe thermal transitions of solutions that contain phospholipid vesicles. Measurements have been made of the properties of dilute aqueous dispersions of dimyristoyl phosphatidyl glycerol, and results have been correlated with previously acquired data on surface films formed from the same materials. Morphological transitions that occur at temperatures above the main gel-liquid crystal transition temperatures have been established.

Analytical theory and computer-based Monte-Carlo calculations have been used to extend a previously developed model for describing the interaction of photons with blood cells moving in the peripheral microvasculature. A diffusion model was used to determine the path length distributions of photons moving within biological tissue, and properties of surface-emitted light have been investigated.

Using a previously devised scheme involving dynamic light scattering to study the gelation and elasticity of polymer networks, measurements were performed to relate mechanical relaxation of networks to their topological and molecular structure. Studies of gelation kinetics have been initiated.

Publications:

Nossal, R.: Network formation in polyacrylamide gels. *Macromolecules* 18: 49-54, 1985.

Steiner, C. A., Litt, M., and Nossal, R: Effects of calcium ions on the structure and rheology of canine tracheal mucin. *Biorheology* 21: 235-252, 1984.

Steiner, C. A., Litt, M., and Nossal, R: Studies of rheologically active biological macromolecules by quasielastic light scattering. *Biorheology* Suppl. I: 335-344, 1984.

Studies on the Effect of Solvent Around Biological Macromolecules

Principal Investigator: B. Lee, Ph.D. (DCRT/PSL).

Solvent can generally influence the behavior of macromolecules; an example of this being hydrophobic behavior. Statistical mechanical methods have been used to investigate the origin of thermodynamic properties, such as the Gibbs free energy, enthalpy, and entropy, in relation to hydrophobic interactions.

Rigorous statistical mechanical studies of fluid solutions have thus far been made on small molecule systems only. If the water molecules are regarded as simple spherical objects, there is a rigorous statistical mechanical procedure and a promising approximation scheme that can handle objects as geometrically complicated as a globular protein. The procedure is necessarily complicated and involves some heavy programming. These calculations, when completed, will aid in the calculation of thermodynamic properties of proteins in solution.

Publications:

Lee, B.: An anatomy of hydrophobicity. In Eisenfeld, J., and DeLisi, C., (Eds.): *Mathematics and Computers in Biomedical Applications*. North-Holland, Elsevier, 1985, pp. 3-11.

Lee, B.: A procedure for calculating thermodynamic functions of a cavity formation from the pure solvent simulation data. *J. Chem. Phys.* (in press).

Lee, B.: Increase in surface area due to atomic scale roughness. *Biochem. Biophys. Acta* 800: 309-311, 1984.

Lee, B.: On the physical origin of the low solubility of non-polar solutes in water. *Biopolymers* 24: 813-823, 1985.

Mitscher, L. A., Hogberg, T., Drake, S. D., Burgstahler, A. W., Jackson, M., Lee, B., Sheldon, R. I., Gracey, H. E., Kohl, W., and Theriault, R. J.: Isolation and structural determination of siderochelin C, a fermentation product of an unusual Actinomycetes sp. *J. Antibiotics* 37: 1260-1263, 1984.

Development of Apollo Computer System for Modeling Macromolecules

Principal Investigator: B. Lee, Ph.D. (DCRT/PSL). *Also:* B. Brooks, Ph.D., R. Feldmann (DCRT/OD); R. Pastor, Ph.D. (FDA).

With the initial development stage for the Apollo system essentially over, we now are beginning to tackle scientific applications of the system. A complete protein modeling procedure involves prediction of secondary and tertiary structures. We have installed a good secondary structure prediction scheme and a research effort is underway for developing algorithms for predicting tertiary structure.

Instrumental Analysis

Principal Investigator: George H. Weiss, Ph.D. (DCRT/PSL). *Also:* J. T. Bendler, Ph.D. (General Electric); E. diMarzio, Ph.D. (NBS); M. Dishon, Ph.D. (Weizmann Institute); J. A. Ferretti, Ph.D. (NHLBI); R. Gaylord, Ph.D. (Univ. of Illinois); J. E. Kiefer (DCRT/PSL); U. Shmueli, Ph.D. (Tel-Aviv Univ./ Israel).

Mathematical techniques are developed for the analysis of data from the measurement of chemical parameters and for the optimization of such experiments. Work has continued on the development of exact representation of the probability densities that arise in crystallographic analysis. Relevant theory has been developed for such densities in direct methods of phase determination. Numerical techniques have been developed for the analysis of dielectric measurements on certain classes of polymers and proteins. A perturbation theory analysis of nuclear magnetic resonance correlation experiments has been applied to such experiments in the nonlinear regime.

Publications:

Dishon, M., Weiss, G. H., and Bendler, J. T.: Stable law densities and linear relaxation phenomena. *J. Res. NBS* 90: 27-39, 1985.

Ferretti, J. A., Weiss, A. K., and Weiss, G. H.: Errors in the measurement of NOE factors. *J. Magn. Res.* 62: 319-321, 1985.

Shmueli, U., and Weiss, G. H.: Centric, bicentric, and partially bicentric intensity statistics. *Crystal Struct. & Statistics* (in press).

Shmueli, U., and Weiss, G. H.: Exact joint probability distribution for centrosymmetric structure factors. Derivation and application to the sigma1 relation in the space group P1. *Acta Crystall.* (in press).

Shmueli, U., Weiss, G. H., and Kiefer, J. E.: Exact random walk models in crystallographic statistics. II. The bicentric distribution for the space group P1. *Acta Crystall.* A41: 55-59, 1985.

Shmueli, U., Weiss, G. H., Kiefer, J. E., and Wilson, A. J. C.: Exact random walk models in crystallographic intensity statistics. I. Space groups P1 and P1. *Acta Crystall.* A40: 551-560, 1984.

Weiss, G. H., Bendler, J. I., and Dishon, M.: Analysis of dielectric loss data using the Williams-Watts function. *J. Chem. Phys.* 83: 1424-1427, 1985.

Weiss, G. H., and Ferretti, J. A.: The choice of optimal parameters for measurement of spin-lattice relaxation times. III. Mathematical preliminaries for non-ideal pulses. *J. Magn. Res.* 61: 490-498, 1985.

Weiss, G. H., and Ferretti, J. A.: The choice of optimal parameters for measurement of spin-lattice relaxation times. IV. Effects of non-ideal pulses. *J. Magn. Res.* 61: 499-515, 1985.

Weiss, G. H., and Kiefer, J. E.: On the probability density of the envelope of a sum of random vectors. *J. Sound and Vib.* (in press).
Weiss, G. H., and Kiefer, J. E.: Random walks in crystallography. *Adv. Stat. Mech.* (in press).
Weiss, G. H., and Shmueli, U.: Fourier representations of pdf's arising in crystallography. *J. Res. NBS* (in press).
Weiss, G. H., Shmueli, U., Kiefer, J. E., and Wilson, A. J. C.: Fourier series and other representations of crystallographic pdf's. *Crystal Struct. & Stat.* (in press).

Studies in Mathematics and Statistics

Principal Investigator: George H. Weiss, Ph.D (DCRT/PSL). *Also:* D. Ben-Avraham, Ph.D. (Bar-Ilan Univ./Israel); J. E. Kiefer (DCRT/PSL).; S. Havlin, Ph.D. (Bar-Ilan Univ./Israel); H. E. Stanley, Ph.D. (Boston Univ.).

Work has continued on the development of the theory of the transmission and absorption of energy by diffusion in fractal and otherwise disordered media. This class of problems is relevant in the theory of chemical reaction rates.

Publications:

Boccara, N., and Havlin, S.: Dilute Ising model on fractal lattices. *J. Phys. A: Math. Gen.* 17: L547-L549, 1984.
Djordjevic, Z. V., Havlin, S., Stanley, H. E., and Weiss, G. H.: New method for growing branched polymers and large percolation clusters below pc. *Phys. Rev.* B30: 478-481, 1984.
Havlin, S.: Comment on the Aharony-Stauffer conjecture. *Phys. Rev. Lett.* 53: 1705, 1984.
Havlin, S.: Intrinsic properties of percolation clusters and branched polymers. In Family, F., and Landau, D. P., (Eds.): *Kinetics of Aggregation and Gelation.* Amsterdam, Elsevier, 1984, pp. 145-156.
Havlin, S., Ben-Avraham, D., and Movshovitz, D.: Percolation on infinitely ramified fractals. *J. Stat. Phys.* 36: 831-841, 1984.
Havlin, S., Dishon, M., Kiefer, J. E., and Weiss, G. H.: Trapping of random walks in two and three dimensions. *Phys. Rev. Lett.* 53: 407-410, 1984.
Havlin, S., Djordjevic, Z. V., Majid, I., Stanley, H. E., and Weiss G. H.: Relation between dynamic transport properties and static topological structure for the lattice-animal model of branched polymers. *Phys. Rev. Lett.* 53: 178-181, 1984.
Havlin, S., Kiefer, J. E., Weiss, G. H., Ben-Avraham, D., and Glazer, Y.: Properties of the skeleton of aggregates grown on a Cayley tree. *J. Stat. Phys.* (in press).
Havlin, S., Movshovitz, D., Trus, B., and Weiss, G. H.: Probability densities for the displacement of random walks on percolation clusters. *J. Phys. A.* (in press).
Havlin, S., Trus, B., and Stanley, H. E.: Cluster-growth model for branched polymers that are chemically linear. *Phys. Rev. Lett.* 53: 1288-1291, 1984.
Havlin, S., Trus, B., Weiss, G. H., and Ben-Avraham, D.: The chemical distance distribution in percolation clusters. *J. Phys.* A18: L247-249, 1985.
Havlin, S., Weiss, G. H., Ben-Avraham, D., and Movshovitz, D.: Structure of clusters generated by random walks. *J. Phys.* A17: L849-853, 1984.
Hong, D. C., Havlin, S., Herrman, H. J., and Stanley, H. E.: Breakdown of the Alexander-Orbach conjecture for percolation. Exact enumeration of random walks on the percolation backbone. *Phys. Rev.* B30: 4083-4086, 1984.
Majid, I. Ben-Avraham, D., Havlin, S., and Stanley, H. E.: Exact-enumeration approach to random walks on percolation clusters in two dimensions. *Phys. Rev.* B30: 1626-1628, 1984.
Meakin, P., Majid, I., Havlin, S., and Stanley, H. E.: Topological properties of diffusion limited aggregation and cluster-cluster aggregation. *J. Phys. A: Math. Gen.* 17: L975-L981, 1984.
Otterman, J., and Weiss, G. H.: Reflections from a field of randomly located vertical protrusions. *Appl. Opt.* 23: 1931-1936, 1984.
Weiss, G.H.: An appreciation of the work of R.J. Smeed. *Transp. Res.* 19: 85-88, 1985.
Weiss, G. H.: First passage times for correlated random walks and some generalizations. *J. Stat. Phys.* 37: 325-330, 1984.
Weiss, G.H.: Overview of theoretical models for reaction rates. *J. Stat. Phys.* (in press).
Weiss, G.H.: Passage times. *Encyc. Stat. Sci.* (in press).
Weiss, G.H.: Random walks. *Encyc. Stat. Sci.* (in press).
Weiss, G.H.: Saddle-point approximations. *Encyc. Stat. Sci.* (in press).
Weiss, G. H.: Statistics in crystallography. *Encyc. Stat. Sci.* (in press).
Weiss, G.H.: Tauberian theorems. *Encyc. Stat. Sci.* (in press).
Weiss, G.H.: Walds identity. *Encyc. Stat. Sci.* (in press).
Weiss, G. H., and Havlin, S.: Trapping of random walks on the line. *J. Stat. Phys.* 37: 17-25, 1984.
Weiss, G. H., Havlin, S., and Bunde, A.: On the survival probability of a random walk on a finite lattice with a single trap. *J. Stat. Phys.* (in press).

Molecular Forces in Cellular Assembly

Principal Investigator: V. Adrian Parsegian, Ph.D. (DCRT/PSL). *Also:* E. Barouch, Ph.D. (Clarkson Univ./NY); E. A. Evans, Ph.D. (U. British Columbia/ Canada); S. Gruner, Ph.D. (Princeton Univ./NJ); A. L. Harris, Ph.D. (DCRT/PSL); R. P. Rand, Ph.D. (Brock Univ./Canada); D. Rau, Ph.D. (NIADDK); J. Zimmerberg, Ph.D. (DCRT/PSL).

Besides interacting by long-range physical forces, large molecules or membranes often interact by bumping or steric forces due to the mechanical motion of bending or rotating. This past year we solved the difficult problem of formulating such motion and estimating its consequent forces during the simultaneous action of the underlying long-range physical force. We now are making a new kind of correlation between molecular interactions and molecular conformation.

Measurements on forces between DNA double helices reveal very strong attractive forces apparently mediated by restructuring water solvent between molecules and regulated by ion binding to the molecular surface. This attraction in many ways resembles the hydrophobic force usually thought to occur between nonpolar surfaces. It appears to us in the many cases where it has been invoked to explain macromolecular properties

that this force can be due to polar molecules and that it can be the strong, specific, and modulated interaction necessary to explain molecular assembly.

Investigations on lipid systems have now been extended to measuring the work of forming aqueous cavities. We are in the process of relating these energies to those involved in the formation of ionic channels in membrane transport.

Publications:

Evans, E. A., and Parsegian, V. A.: The action of thermal fluctuations on forces within lamellar arrays. *PNAS* (in press).

Gruen, D. W. R., Marcelja, S., and Parsegian, A. V.: Water structure near the membrane surface. In Perelson, A. (Ed.): *Membrane Surfaces.* New York, Marcel Dekker, Inc., 1984, pp. 59-91.

Parsegian, V. A., Rand, R. P., Fuller, N. L., and Rau, D. C.: Osmotic stress for the direct measurement of intermolecular forces. In *Methods in Enzymology.* Academic Press (in press).

Parsegian, V. A., Rand, R. P, and Rau, D. C.: Hydration forces: what next? *Chemica Scripta* 25: 28-31, 1985.

Parsegian, V. A., and Rau, D. C.: Water near intracellular surfaces. *J. Cell Biol.* 99: 196-200, 1984.

Prouty, M. S., Schechter, A. N., and Parsegian, V. A.: Chemical potential measurements of deoxyhemoglobin S polymerization: Determination of the phase diagram of an assembling protein. *J. Molec. Biol.* (in press).

Rand, R. P., and Parsegian, V. A.: Force consideration in model and biological membranes. *Canadian J. Biochem.* 44: 318-337, 1984.

Rand, R. P., and Parsegian, V. A.: Mimicry and mechanism in phospholipid models of membrane fusion. *Ann. Revs. Physiol.* (in press).

Membrane Fusion

Principal Investigator: Joshua J. Zimmerberg, M.D. Ph.D. (DCRT/PSL). *Also:* D. Epel, Ph.D. (Hopkins Marine Station/Stanford University); V. A. Parsegian, Ph.D. (DCRT/PSL); R. P. Rand, Ph.D. (Brock Univ./ Canada); C. Sardet, Ph.D. (Villefranche-s-mer/France); B. Trus, Ph.D. (DCRT/CSL); M. Whitaker, Ph.D. (Univ. College London/England).

Experiments have been performed to examine the hypothesis that submembrane fusion-to-cell membranes is driven by granular osmotic pressure, vesicular swelling, and membrane perforation at the point of contact between granular vesicle and cell membrane. The data generated so far are consistent with the idea that a secretory granule must swell to fuse with the plasma membrane and support the hypothesis of an osmotically driven fusion step during exocytosis.

Publications:

Zimmerberg, J., Sardet, C., and Epel, D.: Exocytosis of sea urchin egg cortical vesicles in vitro is retarded by hyperosmotic sucrose: kinetics of fusion monitored by quantitative light-scattering microscopy. *J. Cell Biol.* (in press).

Zimmerberg, J., and Whitaker, M.: Irreversible swelling of secretory granules during exocytosis caused by calcium. *Nature* (in press).

Membrane Transport

Principal Investigator: Joshua J. Zimmerberg, M.D. Ph.D. (DCRT/PSL). *Also:* F. Bezanilla, Ph.D. (UCLA); A. Harris, Ph.D., V. A. Parsegian, Ph.D. (DCRT/PSL).

Techniques have been developed to estimate the internal volume change during opening and closing of ionic transmembrane channels. These involve putting the channel under osmotic stress and measuring the extra work of channel opening in terms of the current-voltage curve or as a bias in the open/closed statistics of a single channel. Preliminary experimental results are inconsistent with traditional blocking or local gating models but support models with major closure of the channel space.

Consulting Services

Principal Investigator: George H. Weiss, Ph.D. (DCRT/ PSL). *Also:* R. Carson, Ph.D. (CC/NM); J. E. Kiefer (DCRT/PSL); A. P. Minton, Ph.D. (NIADDK/LBP); R. J. Nossal, Ph.D. (DCRT/PSL).

Members of the PSL provide consulting services in the physical sciences and applied mathematics. Data has been analyzed on the rate at which fits develop after head injury in a group of over 400 head-injured veterans of Vietnam. We have found that three subpopulations can be identified; those who develop fits within a month post-injury, those who develop them at an exponential rate over a period of approximately five years, and those who develop them at a different nonexponential rate after approximately five years. The first two groups have been identified by previous investigators, but the third appears only in the present study and is due to the long follow-up time.

A joint study with Dr. A. P. Minton has been started on the use of overspeeding to accelerate sedimentation equilibrium experiments on the ultracentrifuge.

Personal Workstation Word Processing

Principal Investigator: N. Crawford (DCRT/PSL/PWO). *Also:* M. McNeel (DCRT/PSL); R. Hargett (DCRT/PWO); K. Griffin (DCRT/OD).

Several word processing packages were evaluated for support by DCRT. DisplayWrite 2 and Multimate were chosen for this role. Work is presently in progress on upgrading DisplayWrite 2 packages to the newly announced DisplayWrite 3. Assistance has been given to interested people at NIH in the form of lectures and demonstrations. Further work has been undertaken on the compatibility of PCs and word processors, as well as on the compatibility of different kinds of word processors.

Computerized Typesetting of Scientific Papers

Principal Investigator: N. Crawford (DCRT/PSL). *Also:* M. McNeel, V. A. Parsegian, Ph.D. (DCRT/PSL); Science Press; Rockefeller University Press; Biophysical Society; Biophysical Discussions.

Our activities during this past year have centered on the transfer of programs originally developed on mainframes to the PC-XT system. It has been found that virtually all required tasks can be done on the personal computer system although processing is much slower.

The interaction of microprocessors with mainframes and the linking of microprocessors have facilitated text transfer and have shown increasing practical value. As an example of the interest generated in this system, we were invited by the editors of *Cancer Investigation* to prepare a description of our procedure. We believe that this project has fulfilled its original purpose and need no longer be listed as an ongoing activity.

Publications:

Parsegian, V. A., Crawford, N., McNeel, M., Douglas, M., and Horton, M.: Electronic submission of scientific manuscripts. *Cancer Investigation* (in press).

Laboratory of Applied Studies

John E. Fletcher, Ph.D., Acting Chief

Clinical Research and Patient Care

Computer-based studies of physiology and pathophysiology during exercise. This project employs breath-by-breath analyses of pulmonary gas exchange performed by a laboratory minicomputer-based system to study oxygen delivery to tissue in normal states and in pulmonary, cardiovascular, and hematologic pathophysiologies. Serial testing of a patient during bicycle or treadmill exercise provides objective indications of severity of disease and efficacy of treatment. Software development essentially has been completed with the addition of various graphical output packages, and the system is in use in protocols for studying patients with sickle cell disease, inflammatory lung disorders, and occupational lung disease.

Computer-based methods of monitoring central nervous system function in critically ill patients. A realtime system employing a super-minicomputer and custom hardware is being developed to assimilate neurophysiological data from patients in the intensive care unit and to display it in a form that allows easy interpretation and timely assessments. The goal of the project is to identify and demonstrate in the clinical environment a system capable of providing reliable objective indices of cerebral function in patients in whom the usual neurologic assessment is difficult. A microprocessor-controlled analog preprocessor has been completed and development of a multitiered digital filtering package is underway.

Computer systems for nuclear medicine. This project involves development and application of computer methods to radionuclide ventriculography, PET scans, and other scintigraphic studies. Application was begun of a logistic discrimination program (LOGISK), developed by A. Albert while a visiting scientist at LAS, to the multiple parameters of regional function in radionuclide ventriculography. The results suggest that a nearly complete separation of normal, diffusely abnormal, and regionally abnormal groups can be achieved when an optimal combination of parameters, identified by LOGISK, is used. Further investigations of the IBM PC-XT graphics systems suggest a use for functional imaging and other image processing applications. The IBM PC implementation of the Graphics Kernel System (GKS) software was found to be unsuitable because it lacks the facility for interactive delineation of areas-of-interest.

Computer analysis of electrocardiograms. The continuing goals of this project have been to evaluate the diagnostic power and epidemiological utility of ECG analysis by computer. ECG data on several thousand cases from the Framingham study have been studied. Of these, five to six percent have echocardiographic evidence for left ventricular hypertrophy. When LVH produces ECG stigmata there is an additive risk factor: a 3- to 5-fold increased risk for coronary disease, a 2- to 6-fold increased risk for myocardial infarct, a 3- to 10-fold increased risk for cerebral failure and a 3-fold increased risk for sudden death. The IBM program has been shown to correctly identify about 75 percent of the cases showing ECG stigmata of anatomical LVH. Reformatting of the Georgetown 12-lead data for the IBM and HP systems is underway so that a comparison of these different analysis techniques can be accomplished.

Laboratory Investigations

Analysis of physiological signals. This project uses minicomputer-based methodology for analysis of physiological signals such as ECG, EEG, and EMG. The loss of critical personnel has impeded expeditious continuation of this project. Nevertheless, redesign of the analysis software to adjust for the difference in the format of the NIAID ECG cart and the higher frequency of the mouse ECGs was accomplished. The entire software package has been moved from the IBM System 370 to the DECsystem-10 computer in order to permit interactive display and analysis.

Network modeling in biology. LAS has shown that network simulation languages operating on the NIH central computer, VAX systems in several Institutes and IBM PCs in individual laboratories provide a powerful modeling tool for NIH scientists modeling neural, hydraulic, and mechanical systems. Manuscripts describing several applications are in press.

Active transport, biochemical kinetics, and their interactions. This project examines experimental and mathematical studies of kinetics and thermodynamics of biological processes involving enzyme-catalyzed reactions. Thermodynamic principles and mathematical analysis are applied, in collaboration with NIH scientists, to problems in membrane transport, bioenergetics, and ligand binding. The principal result has been to provide a sound framework for the interpretation of new experimental results and rational criticism of past approaches. Several manuscripts describing applications have appeared, are in press, and are under review.

Computer Research and Software Development

Mathematical and computational methods for solving nonlinear equations. In FY85, a paper on rapid rootfinding was published that detailed the robust binary search procedure developed at LAS for MLAB. A generalization of this search is now under development. A family of fast Finite Impulse Response digital filters (FIR) are still under development. Several labs at NIH are already using some of them for data acquisition. Dr. Kamgar-Parsi is working to improve a linearly-constrained minimization program, a multivariate rootfinder, and univariate search program. Curve-fitting and weighting methods for improving the robustness of Singular Value Decomposition (SVD) methods for chemical analyses are being studied. New matrix-free methods for solving stiff systems of differential equations are being studied for inclusion in a frequently-used differential equation solver.

Numerical methods for the solution of mathematical models describing reaction-diffusion and other processes in biological systems. This project is concerned with the investigation, development, and implementation of computer methods for the solution of systems of ordinary and partial differential equations (and other mathematical forms) that are used to model steady state and time varying dynamic physiological processes.

This project was severely curtailed in FY85 by the departure of the principal investigator to private industry. A concerted study by a joint DCRT/NIH committee of scientists has reported on the unlikely continuation of this collaborative research activity because of manpower and funding constraints. An attempt will be made to recover some capability in this area through contracts with private industry. Present capability is being maintained only on a limited basis.

Mathematical Modeling of Biological Processes. Quantitative models that describe the relationships between free and facilitated substrate diffusion, metabolism, and microcirculatory flow are being developed and evaluated. These models can identify the critical physiological parameters for substrate supply to tissue and their ranges in normal and pathophysiological states. A new unified model for perfused organ experiments has been submitted for publication. Some new physiologic experiments for model validation are indicated. Additional studies presently concern the resistance to oxygen transport from the red cell interior to the interior of the tissue cell. A number of factors are being reviewed for model inclusion.

Applications of Personal Computers to Laboratory Research. The goals of this project are to determine the applicability of personal computer-based systems in research laboratories, to assemble such systems, and to test them in laboratory investigations. Three differently configured IBM PC-based systems have been utilized in a variety of graphics, numeric computing, communications, and evaluation applications, and have been augmented by a fourth system, a PC-AT professional graphics system. This graphics system will be investigated for its potential use in physiological imaging applications.

Research Projects

Computer-based Studies of Physiology and Pathophysiology During Exercise

*Principal Investigator:*R.C. Burgess (DCRT/LAS).*Also:*M.R. Horton (DCRT/LAS); NHLBI/CHB, PB; NIADDK/LCB.

This project, through a collaborative effort of LAS with the Clinical Hematology and Pulmonary Branches of NHLBI, is directed toward a deeper understanding of the physiology and pathophysiology of oxygen transport to tissues and the development of a clinical tool with a high-degree of sensitivity, through the use of computerized breath-by-breath analysis of gas exchange and computer-based models of ventilation and oxygen transport.

Progress During FY85: A comprehensive computerized exercise laboratory capable of breath-by-breath calculation of respiratory and cardiovascular parameters was established in FY82-84. During the past year several additional facilities have been added:

1. To increase the safety of exercise testing and to provide additional information concerning cardiac response to stress, and an algorithm for arrythmia identification has been developed and tested.
2. More accurate and simpler calibration of mass spectrometer delay has been achieved using computer-controlled solenoid valves to introduce calibration gases and flows.
3. Multiple format (e.g., strip chart, x vs. y, etc.) high-quality graphical output of exercise testing results now can be obtained via a software package written to drive a graphics printer.
4. Programs that compute shunt fraction, steady state validation, and predict oxygen consumption programs have been implemented.

Proposed Course: An expanded protocol to evaluate patients with exposure to inorganic dusts (e.g., silicosis, asbestosis, and coal workers pneumoconiosis) as well as patients with inflammatory lung disease during both bicycle and treadmill exercise is under development. Improvements to the microcomputer system will include online calculation of dead-space to tidal volume ratio and alveolar-arterial gradients.

Publications and Abstracts:

Burgess, R.C.: A Computer Controlled Laboratory for Breath-by-Breath Exercise Testing. *Proceedings of the 20th Annual Meeting of the Association for the Advancement of Medical Instrumentation,* May 1985.

Burgess, R.C.: Computers in the Pulmonary Function Laboratory. *Proceedings of the 50th Annual Scientific Assembly of the American College of Chest Physicians,* October 1984.

Computer-Based Method of Monitoring the CNS in Critically Ill Patients

*Principal Investigator:*R.C. Burgess (DCRT/LAS);*Also:*E.C. Jacobs (DCRT/LAS); CC/Critical Care Medicine.

This project is a joint effort between the Laboratory of Applied Studies and the Department of Critical Care Medicine to design, build, and implement a highly clinically oriented, distributed-processing, minicomputer-based system for analysis and display of scalp-recorded neuroelectric signals. This tool will be used: to investigate the degree of dysfunction in neurologically impaired patients, to correlate the indices developed with other measures of cerebral function, and to evaluate the effectiveness of various therapeutic interventions.

Background and Objectives: In the critically ill patient with multiple organ dysfunction, impaired brain function frequently coincides with deterioration of other major systems. However, the degree of damage and capacity for restoration of the brain does not necessarily parallel that of the rest of the body. In addition, assessment of the central nervous system is hampered by limitations imposed by procedures (e.g., endotracheal intubation) and/or drugs (e.g., Pavulon).

The initial phase of this project is directed toward the development of a comprehensive, mobile, neurodiagnostic system including: a precision analog front-end for low-noise detection, amplification, and filtering of the spontaneous and evoked EEG activity; devices to deliver programmed visual, auditory, and somatosensory stimuli; a central processor with intelligent peripherals for data acquisition, manipulation, calculation, and storage, and a display capable of high resolution graphics and printout for presentation of current and past data, trends, and interpretive imaging.

After initial development and testing has been completed, the system will be used in the Critical Care Unit, Clinical Center, to address the following questions:

- Which electrophysiological parameters can be used to best follow the functional neurologic status of the patients?
- What is the optimal protocol for obtaining data in order to balance recording requirements and nursing care needs?
- How can the parameters best be combined into a meaningful profile and best be displayed to provide comprehensive, yet easy-to-assimilate clinical information?
- How does the information offered by this system compare to other neurodiagnostic techniques?
- How does this system improve care of the patient and understanding of the pathophysiologic dynamics?

Progress During FY85: A multichannel, computer-controlled, distributed-processing, preamplifier/filter designed and prototyped during FY84 has been fabricated and control software has been implemented. This custom peripheral device allows processing from one evoked potential modality to another under program (or manual) control in seconds. Gain at every stage of amplification, from the patient to the ADC, is controlled over a total range of one thousand to ten billion. To preserve latency relationships, linear phase (Bessel function) filters permit selection from eight high-pass and eight low-pass cutoff frequencies. By using the full dynamic range of each stage of amplification and filtering, the highest possible signal-to-noise ratio is insured.

Digital filtering algorithms that implement four approaches to adaptive filtering have been developed and the results have been analyzed on simulated data. A realtime UNIX program to control acquisition, processing, and display on a MASSCOMP minicomputer is partially completed.

Proposed Course: Testing of the filtering algorithms on dogs with known decrements in cerebral perfusion as well as on humans with alterations in mental status will be carried out. The results of the in vivo testing will be used to select the most robust dynamic filtering technique for implementation on the MASSCOMP array processor. These algorithms will serve as the primary waveshaping routines. Secondary routines will be developed to identify and track waveform components that can be used to extract functional information from the electrophysiological data.

Publications and Abstracts:

Burgess,R.C., and Le, H.V.: Filtering of Evoked Potentials, An Integrated Hardware/Software Approach. 11th International Congress of Electroencephalography and Clinical Neurophysiology, August 1985.

Burgess,R.C., Le, H.V., Pottala, E.W., and Bailey, J.J.: A Microprocessor-Controlled Multichannel Preamplifier for CNS Monitoring in the ICU. *Proceedings of the 20th Annual Meeting of the Association for the Advancement of Medical Instrumentation,* May 1985.

Computer Systems for Nuclear Medicine

*Principal Investigator:*M. A. Douglas (DCRT/LAS).
*Also:*B.J. Bunow, J.J. Bailey (DCRT/LAS); CC/Nuclear Medicine; NHLBI/CB.

This project involves computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Nuclear Medicine Department of the Clinical Center and collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiography and myocardial perfusion scintigraphy, renal dynamics, tagged monoclonal antibody studies and pulmonary ventilation-perfusion relationships.

Progress During FY85:

Cardiac Scintigraphy: LOGISK is a multiple group logistic discrimination program developed by Dr. Adelin Albert while a visiting scientist with LAS. This program has been used with the test population on the more than 20 parameters with previously shown ability to detect abnormal cardiac contractility. The three groups represented in the test population are normal, focally abnormal, and diffusely abnormal. The result has been the determination of the optimal minimum combination of parameters for the separation of the three groups represented in the test population. A manuscript detailing these results is currently in preparation.

Gallium Lung Study: The goal of this project is to improve the quality and repeatability of the Gallium Index for lungs, which correlates with active inflammation. The Gallium Index had been determined visually as a ratio of lung uptake to the range of uptake from the high to low uptake regions. Inspection of these indices revealed considerable

variation in the visual evaluations obtained with different observers, and with different contrast settings on the display. An interactive automated system was developed to compute the Gallium Index. There has been no progress in FY85 because the Pulmonary Branch has not assigned someone to continue collaboration on this project.

Desk Top Computers: Image processing is a large resource consumer. Nuclear Medicine involves an increasing volume of images. It would be desirable to find an inexpensive way to distribute additional display capabilities. Investigation indicates that while resolution, pixel depth, and processor speed made the IBM PC-XT inadequate for this purpose, the IBM PC-AT with special third party graphics boards provide a cost effective solution. With 16 to 32 bits per pixel, this combination allows not only the functional imaging possible on the XT but also a wide range of Nuclear Medicine image processing applications. A prototype imaging package is now being developed for both the XT and AT which allow image modification and area of interest delineation. Graphics standard languages are being looked at for future development. Thus far the Graphics Kernel System (GKS) implementation for the IBM PC family is inadequate in that it lacks the mouse/joystick/trackball/lightpen functions necessary for interactive area-of-interest delineation.

Tumor Detection With Monoclonal Antibody Dosimetry Study: A small, known amount of Indium-tagged monoclonal antibody is injected intravenously. The amount and duration of uptake by the liver and spleen is calculated by integrating the counts in the manually delineated liver and spleen and comparing those counts to the counts in a scanned vial of a known amount of Indium. Studies will be directed toward liver and spleen dosimetry as this is the limiting dose in the use of the monoclonal antibodies for the detection of the metastatic spread of tumors such as mycosis fungoides and melanoma. Algorithms have been designed and tested that automatically detect the areas of the liver, spleen, Indium vial, and a background region.

PET Scans and Biokinetics Studies: Investigators from NINCDS, NIMH, NIA, NHLBI, NCI, NIADDK, NICHD, and NIAAA have formed a task force with members of the Nuclear Medicine Department to embark upon a multitude of projects including studies of nerve cell metabolism and receptor function in such conditions as epilepsy, stroke, degenerative diseases (Alzheimers, ALS), neoplastic disease, and Korsakoff's psychosis; studies of ischemia in numerous cardiac conditions; and studies of antibody uptake in tumors. At the request of the Nuclear Medicine staff, LAS is assisting in these studies. Methods for the rapid analysis of large volumes of image data are being investigated. Several commercial products that could be applicable are being studied. These include DISPLAY82 from the Hospital of the University of Pennsylvania and INSIGHT, which is built around Phoenix Data Systems' Solids Engine.

Image Processing: In addition to the image processing activities included in the studies above, a report listing all major image processing facilities at NIH has been published. This directory is designed to facilitate the sharing of solutions to common problems and the solicitation of expert opinions among NIH scientists involved with image processing applications in biomedical research. The work is an outgrowth of the activities of the NIH-wide Image Processing Group, which sponsors seminars on image processing topics.

Proposed Course:

Cardiac Scintigraphy: Work using LOGISK on the test population will be completed and a manuscript detailing the results will be prepared. Efforts will be made to enlarge the test population.

Gallium studies: Further activity on this project is deferred until the Pulmonary Branch, NHLBI reassigns someone to continue collaboration.

Minicomputer and Desktop Usage: The combination of the IBM PC-AT and high resolution graphics boards with color scale depth of 16 to 32 bits per pixel will allow wide usage in image analysis. A system that is under development will be enlarged to include more edge detection, enhancement, filtering and interactive delineation options. It is designed to be a general-purpose interactive imaging system for the analysis of a wide range of Nuclear Medicine

images including cardiac blood pool images, Gallium images, and PET and CT images.

Tumor detection with monoclonal antibody dosimetry study: The package that has been developed for automated liver/spleen dosimetry analysis will need further testing and modification. Future work should include development of systems to assist in the detection of tumors using monoclonal antibodies.

PET Scans and Biokinetics Studies: The Nuclear Medicine staff have requested LAS collaboration in studies of nerve cell metabolism and receptor function, particularly for evaluating data quality and appropriateness of models. Development of new models is anticipated. Because a large volume of image data is expected, further work in the automated delineation of anatomical structures will be carried out through development of fast interactive algorithms and through the purchase and evaluation of commercial packages. When the delineation of structures study has been accomplished, methods for multimodality image comparison will be developed. CT brain images, for example, provide structural information. PET images provide information of function, but are insufficient to show precise geometric structure. Images from these two sources will be compared, structures delineated on the CT image, and the delineations mapped back to the PET image. The next development will be the extension of this from two-dimensions to three-dimensions. These activities should form the basis for a major effort by LAS in the coming years. However, present manpower and staffing limitations are likely to prevent efficient functioning in this important area.

Publications and Abstracts:

Bacharach, S.L., Green, M.V., Vitale, D., Bonow, R.O., Douglas, M.A., Jones, A.E., and Larson, S.M.: Fourier filtering cardiac time activity curves: Sharp cutoff filters. In F. Deconnick (Ed.):*8th International Conference on Information Processing-Medical Imaging.* Den Haag, Nederland, Martinus-Nijhoff, 1984, pp. 266-281.

Bailey, J.J., Douglas, M.A., van Rijk, P.P., Green, M.V., Bacharach, S.L., and Bonow, R.O.: Parameters of regional wall abnormalities from radionuclide ventriculography. *Computers in Cardiology.* Silver Spring, MD, IEEE Computer Society, 1984, pp. 65-70.

van Rijk, P.P., and Bailey, J.J.: Nuclear cardiology. In van Rijk, P.P. (Ed.): *Nuclear Techniques in Medicine.* Den Haag, Nederland, Martinus-Nijhoff (in press).

van Rijk, P.P. Bailey, J.J., Bacharach, S.L., Bonow, R.O., Green, M.V., and Palmeri, S.T.: Computerized methods for detecting regional wall motion abnormalities using radionuclide ventriculography. *European Heart Journal* (in press).

Image Processing. Spring 1985, 34 pp.

Computer-Aided Analysis of Electrocardiograms

*Principal Investigator:*J. J. Bailey, (DCRT/LAS). *Also:*M. R. Horton (DCRT/LAS); Georgetown Medical Center/ ECG Lab.; Framingham Heart Study; Glasgow Royal Infirmary, Scotland.

These studies are directed toward the evaluation of sensitivity, specificity, and predictive accuracy of ECG criteria and the clinical utility, and cost effectiveness of various computer programs. Further studies involve new methods of criteria design by statistical techniques and their use in epidemiological studies as well as clinical practice.

Progress During FY85: The Framingham Heart Study has determined that left ventricular hypertrophy as shown by echocardiography is an independent risk factor for morbidity and mortality. When LVH produces ECG stigmata there is an additive risk factor, viz. 3- to 5-fold increase for development of coronary disease, 2- to 6-fold increased risk for myocardial infarct, 3- to 10-fold increased risk for a cerebral failure, and 3-fold increased risk for sudden death.

ECG stigmata of anatomical LVH show up in about 12 percent of the cases and the IBM program identifies about 75 percent of these. Some of the subjects with ECG criteria for LVH have a normal left ventricular mass. One reason for this discrepancy is the dependence of the criteria upon QRS voltages that are greatly affected by body habits.

Georgetown Medical Center has collected ECGs with the 12 standard leads recorded simultaneously on a series of cases in which the diagnosis of infarct was confirmed by autopsy. The reformatting of this data into 4 groups of 3 simultaneous leads appropriate for the IBM and HP programs was delayed in FY84-85, due to a personnel shortage in LAS, but is now nearly complete.

Proposed Course: The ECG data from Framingham consists of 510 cases with well diagnosed LVH by echo

measurement of LV mass, adjusted for age, sex, and body habitus and over 3700 cases with normal left ventricular masses. Selected parameters from the IBM measurement matrix will be studied using the LOGISK program developed by Dr. Adelin Albert when he was a visiting scientist at LAS. This program will be used to find optimal combinations of parameters to separate these populations.

Mr. John Doue of the Hewlett-Packard Company has offered to process the Georgetown data. However, some additional reformatting of the data will be required before it is compatible with the Hewlett-Packard program; this will be pursued as time and personnel shortages permit. Other programs that might be tested include the Siemens Program developed by Dr. Peter Macfarlane and the Duke University Program, which has a point score method for detecting and grading infarct.

Publications and Abstracts:

Bailey, J.J., Horton, M.R.: Can ECG criteria be standardized? In Willems, J.L., van Bemmel, J.H., Zywietz, C., (Eds.):*Computer ECG Analysis: Towards Standardization.* North Holland Publishing Company, Amsterdam, Netherlands (in press).

Levy, D., Savage, D.D., Garrison, R.J., Bailey, J.J., Kannel, W.B., Castelli, W.P.: Left ventricular hypertrophy: The Framingham study. In Bailey, J.J. (Ed.): *Computerized Interpretation of the Electrocardiogram X.* Engineering Foundation (in press).

Tibbits, P.A., Boccuzzi, S.J., Sandquist, F., Bailey, J.J., Willems, J.L., Bourdillon, P.J., Dreifus, L.S.: A comparison of the Bonner (V2MO) and Marquette 12 SL computer ECG programs. In Bailey, J.J. (Ed.): *Computerized Interpretation of the Electrocardiogram IX.* Engineering Foundation (in press).

Computer-based Analysis and Image Processing in Electron Microscopy and X-ray and Electron Energy Spectroscopy

*Principal Investigator:*M.A. Douglas (DCRT/LAS). *Also:* NIMH/Clinical Neuropharmocology Branch.

This project is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally x-ray micrography and electron energy loss spectra, derived from the electron microscopy images of biological specimens.

Progress During FY85: A manuscript describing results of data collected and analyzed in FY84 is in preparation. This data consists of dense bodies detected in electron micrographs of human blood platelets before and after the addition of fluorine. Progress in FY85 has been limited due to a lack of manpower and the departure of the clinical collaborator from the Clinical Neuropharmacology Branch, NIMH. Work is continuing at a reduced pace on the development of efficient algorithms for the detection and delineation of dense bodies.

Proposed Course: An analysis of phantoms and specimens of known composition is necessary to investigate and quantify changes in the composition of platelets and will proceed whenever additional manpower becomes available. This study will include the formulation of mathematical/statistical models, examination of signal to noise ratios in phantoms and biological specimens, and investigation of the effects of contamination and specimen destruction by the high-energy electron beam. Efforts will continue in the development of algorithms for image enhancement and for automated and interactive element recognition and delineation.

Analysis of Physiologic Signals

*Principal Investigator:*E.W. Pottala (DCRT/LAS). *Also:* NIAID/LPD; FDA/Div. Cardio-renal Drug Products.

This project develops and uses minicomputer signal processing techniques to analyze physiologic signals such as electrocardiograms, electroencephalograms, and electromyograms.

Progress During FY85: Over the years this project has been concerned with physiological signals from diverse sources, such as human ECGs (e.g., Framingham) and electromyograms in myasthenia gravis. The current focus of activity is with rodent ECGs in collaboration with pharmacologists from FDA and investigators from NIAID. However, the part-time engineering technician who supported the interfacing of devices and did systems programming left LAS for private industry in FY84 and was not replaced because of NIH hiring restrictions. The loss of critical personnel has impeded the project's expeditious continuation.

The FDA has collected multiple ECGs on rats who were fed a high lipid diet over several months. The signal analysis methods developed for processing the

FDA rat ECG data have been published. The raw analog data was collected in an uncalibrated form and required preprocessing and conversion to digital format. This task was completed in FY85.

NIAID has isolated pure strains of Trypanosomi cruzi, some of which are cardiotopic and others that attack smooth muscle of the gut. A model of Chagas' disease was achieved using mice infected with these pure strains. In FY84, in midstudy, the air conditioning system in the animal laboratory failed overnight, and as a result many of the mice died from heat stroke resulting in a setback for systematic data collection. The study was restarted with a fresh batch of mice and in FY85 the collection of analog ECGs for the entire experiment was completed.

Because mouse ECGs differ from rat ECGs in frequency content and QRS and ST-T waveform shapes, and because the NIAID cart has a different configuration from the FDA data acquisition system, it was necessary to do some reprogramming of the signal analysis packages. This reprogramming was completed in FY85, as well as moving the software onto the DECsystem-10 from the IBM System 370 .

Proposed Course: The FDA data will be reanalyzed as time and the personnel limitations permit. FDA would also like to study the cardiac effects of hyperthermia, using the new methodology. Feasibility of initiation of these studies depend on adequate staff availability.

Digitization of the analog ECGs and analysis of the NIAID data have begun and will be pursued in accordance with the limitations already mentioned.

The aging MAC-16 system that has been the mainstay of these projects will be replaced with an LSI-11 system with an updated array processor attached. The rodent ECG analysis programs can then be moved from the DECsystem-10 to this minicomputer system, which will facilitate processing and save ADP costs.

Publications and Abstracts:

Le, H.T., Van Arsdel, W.C., Makowski, A., Pottala, E. W., and Bailey, J. J.: Automated analysis of rodent electro-and vectorcardiograms. *IEEE Biomed. Trans.* 32:43-50, 1985.

Yaar, I., Mitz, A.R., and Pottala, E.W.: Fatigue trends in and the diagnosis of myasthenia gravis by frequency analysis of EMG interference patterns. *Muscle & Nerve* 8:328-335, 1985.

Mathematical Models of Binding Equilibria

*Principal Investigator:*J.E. Fletcher (DCRT/LAS).

The objective of this project is the study of mathematical models of ligand-receptor or ligand-macromolecule binding studies at equilibrium. The models are examined for mathematical as well as for conceptual validity, and the models are explored parametrically to determine their suitability for fitting to experimentally obtained laboratory data. The appropriateness of various model fitting criteria are studied and general guidelines and computational algorithms are designed for computer-aided interactive model fitting.

Progress in FY85: No new analytical models were examined in FY85 although a number of manuscript and procedure critiques requested by professional journals and NIH investigators were honored. Requests for copies of exportable computer algorithms continue to be honored and a number of Institute consultations were provided. The principal investigator continues to serve as a consultant, lecturer, and literature reviewer in this area.

Proposed Course: Consultations on new methodology and data analysis will continue to be made as they are requested by collaborating laboratories. Analytical development of new models and continued research in fitting methodology will be limited because of staffing loss and administrative demand on the principal investigator's time.

Mathematical Modeling of Substate Transport in Physiological Environments

*Principal Investigator:*J.E. Fletcher (DCRT/LAS).
*Also:*Louisiana Tech. Univ./Dept. Biomedical Engineering; NHLBI/LB.

Mathematical models of microcirculatory structure and function are developed from conceptual models into systems of coupled ordinary and/or partial differential equations. Methods of solution of these nonclassical formulations are developed and tested, and satisfactory

cost effective methods are used to explore the properties of these models. The model simulations are interpreted in terms of microcirculatory physiology.

One objective of this project is to study whole organ response and organ tissue level phenomena by means of mathematical models in an effort to determine relationships between variables that govern the organ response to physiologic challenges.

Progress in FY85: Investigations were completed for the modeling and analysis of red cell-free perfused organ experiments. The new model was found to be satisfactory for compatibility with the experimental design. This model included capillary diffusion effects and examined the effects of a varying capillary wall permeability. Manuscripts describing a number of parametric studies with this model appeared in print. An extensive manuscript summarizing the results has undergone several reviews and some expanded physiological experiments have been requested. This report is now being revised according to reviewers' requests.

Additional investigations of models of mitochondrial oxygen uptake are being carried out and the results indicate that a number of controlling factors may be involved. The question of resistance to oxygen transport across an unstirred diffusion layer requires considerable reexamination. Model studies have examined unstirred layer effects and spatial distribution of cell spacing. Manuscripts describing these efforts have been submitted for review.

Proposed Course: Research into the above areas will continue in FY86, but at a much reduced level because of Division and Laboratory administrative demands on the principal investigator's time.

Publications and Abstracts:

Fletcher, J.E., and Schubert, R.W.: Capillary wall permeability effects in capillary-tissue structures: In Bruley, D., Horton, C., and Buerk, D. (Eds.): *Oxygen Transport to Tissue-VI.* New York, Plenum Press, 907-917, 1984.

Fletcher, J. E., and Schubert, R.W.: Diffusional Coupling and Wall Permeability Effects in Perfused Capillary-Tissue Structures. *J. Math. Biol.* (in press).

Fletcher, J.E., Schubert, R.W., and Reneau, D.D.: An analytical model for axial diffusion in the Krogh cylinder: In Bruley, D., Horton, C., and Buerk, D., (Eds.): *Oxygen Transport to Tissue-VI.* New York, Plenum Press, 433-442, 1984.

Network Modeling in Biology

*Principal Investigator:*B. Bunow (DCRT/LAS). *Also:*E.W. Pottala (DCRT/LAS); Medical College of Virginia; NIOSH; NIADDK, LMB; DCRT/LSM; NINCDS/LNC.

This project involves evaluation, application, and support of network modeling languages for the description and simulation of complex biological models.

Background and Objectives: Mathematical modeling in biology is especially difficult because of the need to be familiar with both the biological basis of the problems and the mathematical tools required for their solution. Network modeling, supplemented with effective languages for describing the models on computers, largely obviates the need for extensive mathematical sophistication, and makes the process of model formation and testing accessible to biologists lacking such skills. Topological modeling is particularly appropriate to biological problems because the objects of study generally satisfy essentially topological conservation laws. In biological systems, the processes of flow, accumulation, and chemical transformation are fundamental; these are likewise the basic operations in network modeling.

Significance for Biomedical Research: The choice of a model for a biological process strongly conditions the design of experiments to confirm and test it. By making the analysis of models sufficiently simple, flexible, and powerful, we permit an investigator to consider alternative models, including those that include his fullest conceptualization of the biological phenomena. For example, in neuronal modeling, an anatomically-based model for the entire dendritic field of a CNS neuron has been constructed and validated by comparison to experimental measurement. The computer representation could then be subject to new experiments providing the basis for a more complete understanding of neuronal functioning and for further experimental investigation.

Progress During FY85: The latest versions of SPICE have been installed on a number of VAX computers in several Institutes, as well as on an IBM PC.

An anatomically-based model of the dendritic field of a CNS neuron has been developed in collaboration with

LNC, NINCDS. Subthreshold voltage levels and AC impedance and transfer characteristics have been measured in the model and shown to match nicely with experimental data.

A computationally efficient representation of an active (Hodgkin-Huxley) neuronal membrane has been developed and validated. This research has been presented internally, and accepted for publication. SPICE now is available on the IBM PC-XT. Testing has revealed that it is approximately five times slower than the VAX, and is seriously limited as to model size. Nevertheless, there is a range of problems, particularly relating to model development, for which this approach is quite well suited.

Future Course: This project will terminate due to the departure of the principal investigator in FY85.

Publications and Abstracts:

Bunow, B., Peusner, L., Mikulecky, D.C., and Caplan, S.R.: Unifying Graphical Approaches to Dynamic Systems. *J. Chem. Phys.* (in press).

Bunow, B., Segev, I., and Fleshman, J.W.: Modeling the electrical behavior of anatomically complex neurons using a network analysis program: excitable membrane. *Biological Cybernetics* (in press).

Segev, I., Fleshman, J.W., Miller, J.P., and Bunow, B.: Modeling the electrical behavior of anatomically complex neurons using a network analysis program: passive membrane. *Biological Cybernetics* (in press).

Analysis of Coupled Transport and Biochemical Kinetics

*Principal Investigator:*B. Bunow (DCRT/LAS). *Also:* University of Virginia/Medical College; NHLBI/LB.

This project investigates two fundamental problems in biology: the kinetics of enzymes located in cell membranes, and the thermodynamics of bioenergetic mechanisms in mitochondria. Mathematical analysis, simulation on digital computers, and numerical solution of nonlinear algebraic and differential equations are the main tools in these investigations. While these problems are diverse in their biological background, they all share in a common basis of mathematical and physical content in the role played by conservation laws and in the mathematical methods involved in their resolution.

- The Kinetics of Enzymes in Membranes

Background and Objectives: Studies of the mechanism of membrane transport and energy transduction by enzymes in membranes are generally less conclusive than studies of the mechanisms of isolated enzymes. This uncertainty arises because it is difficult both to manipulate the environment of the interior of a biological membrane and to measure responses there. The objective of this project is to determine the extent to which the actual organization of membrane-associated, enzyme-catalyzed processes can be correctly inferred from the application of models, either detailed or phenomenological, to the kinds of experimental measurements currently made.

Significance for Biomedical Research: Studies of membrane-associated enzymes, such as those of mitochondria, for example, are made by measuring external concentration changes, from which one attempts to infer the biochemical mechanism. This process is evidently unreliable, as witnessed by a decades-long controversy over almost every detail of the mechanism. A consequence of our work is to suggest strongly that this lack of reliability is intrinsic. It is a result of incompatibility between the essentially macroscopic nature of the experimental observations, on the one hand, and the molecular character of the questions that are posed, on the other hand. For this reason, the problem is not to be resolved by performing yet another experiment of the kinds currently popular, no matter how ingenious.

Progress During FY85: A manuscript describing the fundamental physics of coupled processes has been accepted for publication.

Future Course: This project will terminate because of the departure of the principal investigator in late FY85.

Publications and Abstracts:

Peusner, L., Mikulecky, D.C., Caplan, S.R., and Bunow, B.: Unifying Graphical Approaches to Dynamic Systems. *J. Chem. Phys.* (in press).

- Thermodynamics of Bioenergetic Systems

Background and Objectives: The mechanism by which the generally reduced components of nutrients are oxidized in mitochondria is still elusive, although most of the components of this pathway have been identified. The membrane association of the components makes it difficult to proceed in the usual biochemical manner of molecular dissection and

reconstitution. Most experimental studies are made on systems that are quite structurally complex. Nevertheless, interest focuses on the usual biochemical question: What is the sequence of molecular forms involved in the bioenergetic pathway? The role of the electron donor, ubiquinone, in this pathway is the particular object of our interest in this project.

Significance for Biomedical Research: An understanding of the mechanism of the central energy-yielding process of living organisms is clearly essential. Thermodynamic analysis has shown that the accepted explanation for the phenomenon of oxidant-induced reduction of cytochrome b in the presence of antimycin cannot be correct. Presentation of a sound physical basis for analyzing multielectron transfer reaction will assist many groups working on this problem who previously have accepted an invalid argument.

Progress During FY85: One manuscript describing this work has been published; two others are in review, and another is in preparation. A working group on the applications of thermodynamics to bioenergetics has been formed, involving personnel from LAS, NHLBI, and NIADDK. The efforts of this group have led to additional manuscripts in preparation.

Future Course: This project will terminate because of the departure of the principal investigator in late FY85.

Publications and Abstracts:

Hendler, R.W., Bunow, B. and Rieske, J.: Thermodynamic and Kinetic Considerations of Q-cycle Mechanisms and the Oxidant-Induced Reduction of Cytochromes b. *J. Bioenergetics and Biomembranes.* 17:51-64,1985.

Mathematical and Computational Methods for Solving Nonlinear Equations

*Principal Investigator:*R.I. Shrager (DCRT/LAS).
*Also:*NHLBI; NIADDK/LBM; NINCDS/IRP; University of Maryland/Computer Science Dept.

Methods are developed for solving nonlinear equations frequently encountered at NIH. These equations are usually encountered in the context of constrained nonlinear least squares problems or in the numerical solution of nonlinear differential equations. Related problems, such as asymptotic error analysis and the efficient treatment of sparse matrix systems, are also considered.

Progress During FY85: In the course of analyzing the behavior of the cytochrome chain, both equilibrium and kinetic studies have produced new findings. Through an SVD analysis developed at LAS, two-electron carriers were detected where only one-electron carrier had been found by previous investigations. Using specially-designed digital filters for correction of electrode delay time, also designed at LAS, the kinetics of proton extrusion from respiring vesicles is seen to produce a burst of protons in the first 0.3 seconds of respiration. This behavior differs radically from that predicted by standard assumptions. Totally new flow-cell apparatus is now being designed to experimentally confirm this last finding. Papers on both the equilibrium and the kinetic studies have been submitted for publication, and a paper on the kinetics was presented at the FASEB meeting in Anaheim.

A new function of an interval of floating point numbers, called the ordered selector, with software being developed at LAS, promises to improve the efficiency of some common searches for roots and minima of functions. A specialized version was produced here in 1983, described in the 1985 article "Rapid Robust Rootfinder"in *Math. of Computation.* A more general version should be ready for testing in FY86.

Dr. Behrooz Kamgar-Parsi is working to improve a linearly-constrained minimization program, a multivariate rootfinder, and a univariate line search program. His new branch-and-bound algorithm was published this year.

Digital filtration by staging, developed at LAS, has proven of use to several investigators. It allows the data to be smoothed by steps and compared to the original data to insure fidelity. At the same time, its computation time is proportional to the log of the length of the overall filter, putting its efficiency in a class with FFT and other fast transforms, without direct reference to the frequency domain. A manuscript describing these findings has been submitted.

The SVD analysis of titration and kinetics, developed here in 1980, has generated some additional activity in the literature. Several papers have appeared using the analysis, while others have recommended alternatives

or improvements. A survey of work in this area now is being written here that will also serve as a tutorial and a manual of good practice, incorporating the merits of the recent work.

Proposed Course: Most of the active areas of computation in LAS involve vectors and matrices, often of considerable size. With the proposed acquisition of an FPS164 array processor comes the possibility of a considerable improvement in processing speed. In addition, the system will handle large problems that currently have to be scaled down with attendant loss of resolution. But with increased problem size comes the increased effects of ill-conditioning in its various forms (i.e., more rapid computation of more and larger numerical errors). It will be our task to procure, produce, and advertise sound methods in the handling of large problems, particularly in the areas of orthogonalization and large systems of differential equations. Projects involving rootfinding, filtering, and SVD are expected to remain active. Dr. Kamgar-Parsi will be leaving for a university position, but will be retained as a guest worker into FY86.

Publications and Presentations:

Hendler, R.W., Setty, O.H., Shrager, R.I., Bunow, B.J., Fletcher, J.E., Reynafarge, B. and Lehninger, A.L.: Real-Time measurements and the H/O ratio for succinate oxidation. An early H burst. *Federation Proc.* 44: 1081, 1985.

Kamgar-Parsi, B., and Kanal, L.: An improved branch-and-bound algorithm for finding K-nearest neighbors. *Pattern Recognition Letters* 3: 7-12, 1985.

Shrager, R.I.: A rapid robust rootfinder. *Mathematics of Computation* 44: 151-165, 1985.

Shrager, R.I.: Optical spectra from chemical titration: An analysis by SVD. *SIAM J. Algebraic & Discrete Methods* 5: 351-357, 1984.

The Solution of Reaction-Diffusion Systems in Biology

*Principal Investigator:*M. Bieterman (DCRT/LAS).*Also:*J.E. Fletcher (DCRT/LAS); I. Babuska (Univ. of Md.); D. Covell (NCI/LMB).

This project consists of the development of numerical methods and mathematical software for the solution of partial differential equations describing dynamic physiological processes. Adaptive finite element techniques have been generalized and used for models of nerve conduction, oxygen transport in tissue, uptake of macromolecules into the lymphatic system, and in preliminary studies of subsurface contaminant flow. FORTRAN-coded packages implementing these and other techniques are available for use on the major DCRT computers.

Progress During FY85: The principal investigator on this project left for private industry in early FY85. The software described in last year's report is being maintained in an active status, but research in this area has been halted.

Proposed Course: This project will remain active only at a minimal level until new technical staff can replace the principal investigator.

Publications and Abstracts:

Bieterman, M.B., and Babuska, I.: An adaptive method of lines with error control for nonlinear parabolic equations of the reaction-diffusion type. *J. of Computational Physics* (in press).

Personal Computers in the NIH Research Environment

*Principal Investigator:*M.R. Horton (DCRT/LAS). *Also:*R.C. Burgess, M.A. Douglas, B.J. Bunow, E.C. Jacobs (DCRT/LAS); Personal Workstation Office (DCRT/OD).

In this project, a variety of personal-computer-based systems is assembled and investigated for their utility as research tools. In general, research projects often require such activities as laboratory data acquisition and analysis, physiological imaging, mathematical modeling, and numerical analysis. Commercially available hardware and software components of microcomputer systems purport to be highly advantageous in such research systems and need critical examination and evaluation to determine their true capabilities and appropriate use. This examination is the objective of this project.

This project is designed to determine appropriate uses for personal computers in the research laboratory, and to develop prototype personal-computer-based systems to achieve research objectives including laboratory data acquisition, analysis, and display.

Background and Objectives: Because the technological advances in microcomputer architecture are occurring so rapidly, the peripheral equipment and software needed for laboratory applications continue to appear

on the market in explosive fashion. The evaluation and selection of available, useful equipment and software, and the development of microcomputer-based laboratory systems are the objectives of this project.

Significance of Biomedical Research: Microcomputer-based laboratory systems, if configured with appropriate peripheral data acquisition and display equipment and software can bring the power of computing tools into the hands of biomedical researchers. Discovery of the appropriate balance of mainframe and personal computing will lead to increased utilization of powerful research tools while helping to hold down costs of research.

Progress During FY85: Three personal-computer-based systems have been used in a variety of laboratory activities:

- as a tool for generating and evaluating digital filters, as an intelligent terminal or bridge between many disparate computer systems (e.g., IBM System 370, LSI 11, DECsystem-10, MASSCOMP)
- as a developmental device for low-level operating systems routines (e.g., function parsers, symbol table manipulators, command parsers, error handlers)
- as a desk-top system for evaluation, management and display of laboratory data, and
- as a tool for preparing slides and artwork for papers presented to professional societies.

In addition, evaluations of language compilers and graphics/imaging capabilities continued in conjunction with and at the request of the Personal Workstation Office. Several laboratory members are serving as experts for other NIH laboratories and investigators in various areas of personal computer use.

Future Course: With the acquisition of an IBM PC-AT Professional Graphics System, development of a useful laboratory imaging system will be pursued. Evaluation of new hardware and software products will continue. Utilization of the personal computer systems in ongoing laboratory projects will continue to provide experienced laboratory personnel who can serve as advisors and information sources for other NIH investigators.

Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

LSM activities can be divided into three areas: computation, consultation, and research.

Computation

A major part of LSM activity is the offering of statistical and mathematical systems/packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does support a system/package for the NIH community, it provides maintenance, documentation, instruction, and assistance for users to interpret the results.

Statistical Systems/Packages Support. During this year, the Statistical Software Section of LSM maintained the following program packages and programs:

- BMDP: BMDP Statistical Software, Inc.
- SPSS, SPSS-X, SCSS: Statistical Package for the Social Sciences, SPSS, Inc.
- SAS, SAS/GRAPH, SAS/ETS, SAS/OR, SAS/FSP: SAS Institute, Inc.
- P-STAT: Statistical Package, P-STAT, Inc.
- IMSL: International Mathematical and Statistical Libraries, IMSL, Inc.
- MSTAT1: Collection of Mathematical and Statistical Programs, DCRT.

During the year SAS, SPSS-X, BMPD, PSTAT, IMSL, and MSTAT1 went through a major update. The SSS staff answered over 8,500 calls for assistance, and taught a total of 15 courses on these systems; 2 each on SPSS and BMDP, 8 on SAS and 3 on SAS/GRAPH. A half-day seminar was also offered on PSTAT.

The use of program packages continues to increase. For the first time, the accesses of statistical software exceeded one million in FY85 . The average accesses per month of all the statistical packages rose from around 74,000 during FY84 to over 85,000 in FY85. SAS averaged over 79,000 accesses per month, up from 67,000 per month in FY84. The average number of accesses per month for SPSS and SPSS-X was around 4,600--down from 5,000 in FY84. The BMDP package averaged 1,200 accesses, down from 1,800 in FY84. Accesses to the IMSL and MSTAT1 packages cannot be counted, but are estimated to have increased during FY85.

Support for MLAB. The Biomathematics and Computer Science Section maintains the DECsystem-10 interpretive program MLAB, a package designed and implemented by BCS staff. During FY85, several hundred biomedical researchers at NIH used this package for modeling and graphical display tasks. During FY85, one introductory and one advanced course each were taught for MLAB, plus a special course on MLAB use for modeling of chemical kinetics and equilibria. New MLAB documentation was distributed: the *MLAB Reference Manual*, eleventh edition, the *MLAB Beginner's Guide,* third edition, and the *MLAB Applications Manual*, fourth edition. Two MLAB articles were prepared for *INTERFACE*.

Support for the GRAPH and DNADRAW Systems. The GRAPH system for producing publication-quality graphs on the DECsystem-10 was continued, with increased use. Seven new fonts were added, plus software to fill in and smooth characters of any size. A facility to add titles to shaded areas was added. Four courses on GRAPH were taught. The *GRAPH Reference Manual*, fourth edition, was distributed, and an article on GRAPH appeared in *INTERFACE*.

A DECsystem-10 program DNADRAW was released during FY85, to produce publication-quality diagrams showing long DNA sequences. Three courses in DNADRAW have been taught, and an article on DNADRAW appeared in *INTERFACE*.

Support for the VMAP System. An S/370 program VMAP for printing scientific text using an IBM 6670 laser printer and a system of fonts and input codes developed in LSM research was released during FY85. This program was designed so that users of the DCRT text editor WYLBUR can obtain camera-ready copy of scientific text with a small amount of additional training. There was an *INTERFACE* article on VMAP, and a VMAP course was given in the latter part of FY85. The *VMAP Reference Manual* is now being printed.

Support for Other Software. BCS continues to maintain certain special-purpose software and give

limited assistance to users on request. Version 3.0 of the REDUCE program (Rand Corp.) was released, and an article on REDUCE appeared in *INTERFACE*. This program facilitates symbolic computation for algebraic expressions or matrices. Various LSM-created programs for analysis and reconstruction of biological shapes by the symmetric axis method were retained, but not used, during FY85. A program for interactive construction of a document index was discontinued due to the departure of its creator.

Consultation

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are successful and are brief precisely because there is a known answer to the question posed. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

LSM consultations in FY85 were of the following types:

- Mathematical, statistical and computer science advice with limited computer use (5 percent).
- Mathematical or statistical advice with considerable computer use (55 percent).
- Computational advice alone (40 percent).

The large computer use in these figures results from the continued availability and use of general purpose statistical and mathematical packages like SAS and MLAB. These percentages are unchanged from last year.

The diverse nature of LSM consulting is indicated by the projects and activities listed below.

Clinical Research, Patient Care, Epidemiology

Effect of Chlorambucil on Primary Biliary Cirrhosis. J. Hoofnagle (NIADDK/DD). Patients with primary biliary cirrhosis of the liver participated in a randomized trial to evaluate the drug chlorambucil. LSM provided analysis of the data from this experiment and in particular devised a nonparametric procedure to evaluate the effect of the drug from repeated liver biopsies.

Effect of Metoclopramide on ERGs. M. Jaffe (NEI/CB). Electroretinograms (ERGs) are obtained from patients on and off the drug metoclopramide to assess its effect on vision. LSM provided the model for a repeated measures analysis as well as nonparametric procedures to study the changes of various parameters of ERGs.

Thyroid Stimulating Hormone Study. Dr. Hans Agren (NIMH/LCS). A multivariable study of the connections between several hormone levels and sub-diagnoses of depression was performed. TSH (Thyroid Stimulating Hormone) and changes in TSH were examined before and after adminstration of TRH, along with changes in cortisol, to examine their relatedness to endogenous (biological) depression. Test scores consisted of several measures of depression and weight loss. The analysis was based on an unbalanced ANCOVA (analysis of covariance) and used the cell means model to provide a non-data dependent test of hypotheses.

Parkinson's Disease Study. Dr. Erich Mohr (NINCDS/MN). Neurobehaviorial (cognitive) correlates were studied in connection with the administration of L-Dopa in patients with Parkinson's disease. Each patient was used as his or her own control, and a repeated measures model was applied, with the novel complicating feature of a multivariate response (dependent) variable.

Laboratory Investigation

Lipid-Protein Interaction. R. L. Deutsch (NIADDK/LCP). Vibrational spectra of membrane assemblies are obtained by means of Raman spectroscopy. LSM assisted in using MLAB for computation of Fast Fourier Transform, filtering, and inverse Fourier transform. Using this analysis, spectra were retrieved from noisy signals. Acquisition times were substantially reduced (from 48 hours to 1 hour), leading to better utilization of the instruments and reduction of artifacts resulting from system drift.

Drug Toxicity Suppression Study. R. C. Chen (NHLBI/IR/LC). Drug toxicities of certain kinds are suppressed by addition of GSH to cells. Time course of covalent binding of reaction intermediates was studied.

LSM assisted in using MLAB to formulate and analyze a complex pharmacokinetical system of equations modeling the system.

Vasogenic Brain Edema in Rabbits. T. Kuroiwa, R. Cahn, I. Klatzo (NINCDS/LNNS). The water content is investigated in brain tissue of rabbits that have been subjected to a hypertensive insult that breaches the blood-brain barrier. The specific gravity of tissue samples were compared at different sacrifice times after the insult using a stepwise treatment versus control procedure. A model was developed by LSM that predicts specific gravity of brain tissue based on the amount of extravasated serum albumin present at varied times after the insult. Computer-generated publication-ready graphs also were provided.

Atherosclerosis in Swine. H. Kruth, J. Cupp (NHLBI/EA). The build-up of foam cells on the interior wall of the hearts of young male swine was measured using flow cytometry techniques. Swine on four different diets were sacrificed at varied times for study. LSM provided the sampling design as well as the analysis, including a stepwise nonparametric multiple comparison procedure to assess the effect of the diets for different lengths of time. A correlational analysis confirmed the design to compare diets using litter mates. In a separate study, the foam cell density was measured in swine of varied ages fed a controlled diet in order to assess spontaneous disease. A nonparametric analysis studied the relationship of age and foam cell density, suggesting a division of swine into two groups of foam cell responders. Using the genetic relationships of these inbred swine, a large-sample weighted U-statistic theory was developed to study the genetic relationships of the two groups and was confirmed with a computer simulation.

Optical Dichroism Response. A. Stone (NIMH/LNB). LSM continued to assist in designing and evaluating models designed to predict structural properties of protein molecules by analysis of optical dichroism data.

Genetic Linkage Analysis. J. Silver (NIAID/LMM). Analysis of genetic linkage was done using recombinant inbred strains of mice. LSM assisted in calculating the confidence limits using REDUCE, a system for symbolic and algebraic computation.

Receptor Gene DNA Sequence Study. W. J. Leonard (NCI/MET). The DNADRAW program was used to prepare sequences of the human interleukin-2 receptor gene for publication. Interesting subsequences, such as polyadenylation signal sequences, were highlighted using this program.

Rabbit cDNA and Genomic DNA Sequences. R. Mage (NIAID/LI). The DNADRAW program was used to prepare sequences of rabbit cDNA and genomic DNA for publication, with automatic highlighting of information subsequences. One sequence encodes the B chain of the important antigen-specific receptor of rabbit T cells. A paper containing this figure will appear in the *Proceedings of the National Academy of Sciences.*

Effect of Alcohol on Fish Muscles. M. Pollard (NIADDK/LCBG). Earlier work showed that fish intoxication by alcohol increases with addition of caffeine. In order to study the effect of alcohol on isolated muscles, the content of free calcium is varied in the Ringer perfusion solution using a sequestering agent EGTA. LSM assisted in iterative calculations of the thermodynamic affinity constant for calcium binding and preparation of graphs, using MLAB.

Drug Binding Study. B. Cohen (NIADDK/LBP). Tests were performed on organophosphate binding to ACH receptors in frog muscle. LSM assisted in estimation of rate constants by curve-fitting a double-exponential model using MLAB.

Nerve Membrane Ionic Currents. B. Cohen (NIADDK/LBP). Measurements of ionic currents in nerve membranes show noise patterns revealing useful information about timing and mechanism of the opening and closing of ion channels. LSM assisted in analysis of frequency spectra of membrane current noise, using Fast Fourier Transform and curve-fitting analysis performed with MLAB.

Computer Research and Technique Development

Curve-Fitting Methods. A. Minton (NIADDK/LBP). LSM assisted in the selection and adaptation of curve-

fitting algorithms for data analysis using a programmable calculator.

Signal Processing. M. Unser (DRS/BEIB). Testing was done of fast filtering algorithms using modified Fourier transforms together with verification of properties of some special kinds of matrices. LSM assisted in formulating routines using REDUCE to perform computations for complex matrix algebra and to generate orthogonal Fourier transform matrices.

Research

Automated Data Processing of Medical Language

*Principal Investigator:*M. G. Pacak (DCRT/LSM). *Also:*A. W. Pratt (DCRT/OD); G. Dunham, S. Harper (DCRT/LSM); D. Henson (NCI/DCPC).

Research in medical linguistics continued, including the establishment of patterns of compositional lexical semantics of medical terms and the development of a comprehensive lexicographic data base for the modeling of categorized nomenclatures using partially ordered sets.

Research also continued in development of a comprehensive lexicographic data base for the modeling of categorized nomenclatures.

Collaboration continued with the Laboratory of Pathology, NCI, and the DCRT Data Management Branch to maintain and improve the data base of the Clinical Center surgical pathology report.

The automatic encoding system provided by MIS uses multiple word/phrase matching dependent on morphological analysis and other linguistic techniques to provide full SNOP encoding for English pathology diagnostic statements. Statements in this representation language convey the site and tissue of the specimen, the specific morphologic and histopathologic diagnoses, and etiologic agents.

The encoding programs were updated by incorporating the theory of syntax for diagnostic noun phrases developed earlier. This increased the interplay of syntactic and semantic criteria in analysis, and enabled more thorough treatment of discontinuous sequences and improved precision for encoding of adjectives.

Collaboration continued with Dr. Donald E. Henson (NCI/DCPC/CORB). Work continued on specific areas of the dictionary along the lines established for the lymphoma vocabulary.

Work also continued on the creation of a comprehensive lexicographic data base relating the body of medical nomenclature and vocabulary to itself and to the structure of existing coding systems. The goal is the semi-automatic display of relevant relationships of one dictionary system to another, the merge of dictionaries, and the construction of medical microglossaries for medical language data processing.

Publications:

Dunham, G. S.: The Role of Syntax in the Sublanguage of Medical Diagnostic Statements, in Sublanguage. In Grishman, R., Kittredge, R. (Eds.): *Description and Processing*. Hillsdale, NY, Lawrence Erlbaum Associates (in press).

Dunham, G. S., Henson, D. E., and Pacak, M. G.: Three solutions to problems of categorized nomenclatures. *Methods of Information in Medicine* 2: 87-95, 1984.

Cluster Analysis

Principal Investigator: M. B. Shapiro (DCRT/LSM). *Also:*J. Wunderlich, J. Titus (NCI/DCBD/I).

The main objective of this project is the application of computer cluster analysis and related methods to NIH research problems.

Cluster analysis was applied to find the location of clusters in cell sorter data. Up until now this work has been done by drawing contour plots of three variables at a time. The cluster analysis techniques allow a large number of cell sorter variables to be analyzed at once, and should give a more accurate result. Work with Dr. John Wunderlich and Julie Titus is continuing.

Techniques developed under this project have been implemented in the GRAPH and DNADRAW computer programs for publication-quality graphics presenting multivariate data and DNA sequence data.

Publications:

Shapiro, M. B., and Knott, G. D.: C-LAB, an Interactive System for Cluster Analysis. *Proceedings of the 17th Symposium on the Interface.* Lexington, Kentucky, 17-19 March, 1985.

Shapiro, M. B., Schein, S. J., and DeMonasterio, F. M.: Regularity and structure of the spatial pattern of blue cones of macaque retina. *J. Amer. Stat. Asso.* (in press).

Shapiro, M. B., and Senapathy, P.: Automated preparation of DNA sequences for publication. *Nucleic Acids Research* (in press).

Research Topics in Computer Science

Principal Investigator: G. D. Knott (DCRT/LSM).

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is very useful, because such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

In FY85, work continued on the analysis of trie data structures and the development of algorithms and analysis for a new type of doubly-chained trie capable of holding prefixes.

This work is of particular importance for text storage and retieval, including dictionaries, indices to document collections, and various special thesari. The proposed data structure provides a general mechanism for storing arbitrary words and/or phrases without restriction on content. The storage scheme is fast and parsimonious, and the retrieval scheme is also fast. Prior to discovering how to handle prefix items, tries could not be as easily employed for arbitrary collections of words.

Publications:

Shapiro, M. B., and Knott, G. D.: C-LAB, an Interactive System for Cluster Analysis.*Proceedings of the 17th Symposium on the Interface.* Lexington, Kentucky, 17-19 March, 1985 (in press).

Discrete Mathematics and Applications

Principal Investigator: G. Hutchinson (DCRT/LSM).

The study of the algebraic structure of submodules of product modules M x M was revised and extended. Additional results were obtained in the case of vector spaces. Work is continuing in the analysis of these structures.

In previous work under this project, the VMAP system for describing scientific text was developed. During FY85, a computer software system for generating scientific manuscripts by VMAP methods was made available to users of the NIH Computing Utility. Further development of VMAP methods is continuing, and it is expected that more powerful versions of VMAP will be made available incorporating the new methods. In particular, the expected replacement of the IBM 6670 laser printers by IBM 3800 model 3 and 3820 laser printers will create many new opportunities for general-purpose software for generation of scientific documents.

Publications:

Hutchinson, G.: Representations of additive relation algebras by modules. *J. of Pure and App. Algebra* (in press).

Multivariate Statistical Analysis

Principal Investigator: J. E. Mosimann (DCRT/LSM).
Also: J. N. Darroch (Flinders University, Australia).

The objective of this project is the study of multivariate ratios or proportions.

Study continued on multivariate statistical methods for analyzing ratios that follow a multivariate lognormal distribution. Studies of random properties that follow mixtures of Dirichlet distributions were undertaken. Problems of maximum likelihood estimation for these models were resolved, and computer programs were written to implement these estimation procedures. Two papers are being prepared in this work.

Publications:

Darroch, J. N, and Mosimann, J. E.: Canonical and principal components of shape. *Biometrika* (in press).

Linear Methods in Statistics

Principal Investigator: J. D. Malley (DCRT/LSM).

The objective of this project is to study linear methods of statistics and their applications to biomedical research.

Further results have been obtained for the problem of optimally estimating the variance components in an analysis of variance. These new methods now are shown to be ring-theoretic in nature as well as simple to calculate. This underlying algebraic nature of the solutions represents also a new body of technique in the statistical literature, and hence promises a new avenue of research in mathematical statistics generally. The collected material is presently being brought together in a book in preparation, and will provide a

complete overview of the unbiased estimation of variance components as well as help mediate the introduction of algebraic structural methods into the statistical literature.

Collaborative work was completed with Dr. G. Crabtree (NCI/DCBD/LP) on the evolution of the three fibrinogen genes. Several probabilistic models were constructed to deal with the problem of data, which by the nature of the problem is inaccessible to the researcher. Specifically, the pattern of present or absent introns on the genes was studied in an effort to determine the historical development of the genes, and one class of observations is that for which an intron is absent on all three genes, its presence thus being indetectable on the present day genes.

Publications:

Crabtree, G., Comeau, C., Fowlkes, D., Fornace, H. A., Malley, J., and Kent, J.: Evolution and structure of the fibrinogen gene. *J. Mol. Biol.* (in press).

Nonparametric Statistics

Principal Investigator: G. Campbell (DCRT/LSM).

Research is concentrated in several areas of nonparametric statistics with applications to biomedicine.

The study of nonparametric multiple comparisons was continued in FY85. A paper with J. H. Skillings comparing various procedures for determining pairwise differences among treatments has been accepted for publication. The development of distribution-free procedures for data to which weights have been attached is under investigation. The weights arise in biomedical settings through covariates or estimated probabilities or genetic information.

The large-sample theory for weighted U-statistics is being developed and, in a particular application, compared with the computer simulated small-sample distribution. The study of proportions also is being continued. A paper on incomplete correlated proportions recently has appeared. Work is continuing on a general theory for modeling the correlation structure of proportions. These developments along with their accompanying specialized computer programs have many applications to biomedical data expressible as proportions.

Publications:

Campbell, G.: Testing equality of proportions with incomplete correlated data. *J. Stat. Planning and Inference* 10: 311-321, 1984.

Campbell, G., and Skillings, J. H.: Nonparametric stepwise multiple comparison procedures. *J. Amer. Stat. Asso.* (in press).

Computer Graphics and Mathematical Applications

Principal Investigator: K. R. Bhutani (DCRT/LSM).

Project Objective: The major objective is to formulate mathematical and computational techniques and to apply them to problems of biomedical research and computer science.

Progress During FY85: Research during FY85 was concentrated on Boolean algebras in a topos of sheaves on a locale. In particular, the notion of injectivity and related topics was studied and completed. A paper on this research has been accepted by the *Mathematical Proceedings of the Cambridge Philosophical Society.* Two more manuscripts on the study of Abelian groups in a topos of sheaves on a locale are complete except for some minor revisions.

Development of computer software for faster and more flexible computer graphics was investigated in collaboration with LSM staff members. In addition, a study for the development of computer software for symbolic and algebraic calculations was begun.

Proposed Course: Research activity in computer graphics will continue. This will involve using the capabilities of intelligent graphics terminals to simplify mainframe computations.

Development of software for simplifying symbolic and algebraic computations will continue.

Research in mathematics will be concentrated on Boolean algebras and Abelian groups in a topos of sheaves on a locale.

Publications:

Banaschewski, B., and Bhutani, K. R.: Boolean algebras in a localic topos. *Math. Proc. of the Cambridge Philo. Soc.* (in press).

DNA Sequence Analysis and Mathematical Methodology

Principal Investigator: P. Senapathy (DCRT/LSM).

Project Objective: Technical progress in the isolation and sequence analysis of DNA has greatly accelerated the rate of accumulation of new sequences. The use of computers to store and analyze nucleic acid sequence data also has been on the increase in recent times. Computers currently are used in molecular biology for the following purposes: (1) to set up data banks for storage of sequences with specific annotations and comments on the special sequence features; (2) to analyze a given sequence for patterns of restriction enzyme sites, repetitive sequences and potential coding regions; (3) to search for consensus regions having specific biological signals; (4) to search a data bank for sequences homologous to a given sequence; and (5) to perform dot-matrix analyses to determine the evolutionary relationship between homologous sequences.

Several unusual features, such as tandem repetitions, interspersed repetitive sequences, consensus sequence regions, high AT or GC-rich regions, that may have functional significance have been observed recently in natural DNA sequences. A systematic statistical analysis that may bring to light some of the important distribution characteristics of a given subsequence could contribute significantly to the understanding of the DNA sequence repetitions and the distributions of other sequence elements. To this end, we have carried out a systematic statistical analyses of DNA sequences using the sequences available from the data banks and various statistical methods.

Progress During FY85: The systematic computer-aided statistical analyses of DNA sequences from data banks reveal novel characteristics of the distribution of sequence elements in natural DNA sequences. The distribution of waiting-times between successive repetitions of a given sequence element is geometric (rather than normal as frequently assumed). The analyses show that a given subsequence is repeated naturally at very close distances more frequently than at longer distances and that the shorter the distance, the more frequent would be its occurrence in a sequence.

The present data indicate that taking the characteristics of the distribution of its waiting times into consideration is very important in the understanding of the repetitiveness of a given sequence element in DNA. The approach and the analysis described here should help others working in this field to assess the statistical probability of the repetitions of biologically important sequence elements. Further work with statistics in this area may contribute to the understanding of the complexities of sequence repetitions in satellite DNA.

The computer program DNADRAW for computer generation of publication-quality graphics presenting DNA sequences was developed in part from this research.

Proposed Course: The capacity to analyze gel patterns of restriction fragments of a DNA of known sequence using computers is lacking at present and would be very helpful in recombinant DNA research. We are developing a package of computer software that would carry out a number of analyses starting from generating a gel pattern of restriction enzyme fragments from a given DNA sequence or from recombinants of two or more DNA sequences. For example, this package would:

(1) generate linear restriction maps of a given sequence and generate a gel picture containing lanes for the various individual or combinations of restriction enzymes,

(2) generate circular restriction enzyme maps for given DNA sequences and different restriction enzyme sites,

(3) recombine or delete given DNA sequences and carry out the above map and gel analysis.

Development also is envisaged of software to generate restriction enzyme maps of DNAs whose sequences are unknown by using the gel patterns of their fragments. These capabilities are expected to aid in the planning and decisionmaking during the construction and cloning of DNA sequences, and in the studies of deletions, insertions, and site-directed mutagenesis of genes.

Publications:

Senapathy, P., Tratschin, J.-D., and Carter, B. J.: Replication of adeno-associated virus DNA. *J. Mol. Biol.* 179: 1-20, 1984.

Shapiro, M. B., and Senapathy, P.: Automated preparation of DNA sequences for publication. *Nucleic Acids Research* (in press).

Algorithms and Other Methods for Biomathematical Computing

Principal Investigator: J. Pochobradsky (DCRT/LSM).

Project Objective: The major objective of this project is to develop computer algorithms and methods that are useful in biomathematical analysis or display of biomedical data. Implementation of these methods in MLAB is under consideration.

Progress During FY85: Improved methods for generating frameworks with mixed logarithmic and rectangular scales for 2-D data were completed and made available through MLAB. Work on 3-D frameworks is continuing.

Previously-designed algorithms for Kolmogorov-Smirnov statistical tests are being revised and tested against published tables. The purpose of the analysis is to determine whether errors in a set of data follow a normal distribution.

Work is continuing on the design and testing of spline methods for connecting data points by smooth lines. Preliminary calculations have been made using the calculus of variations for curves in parametric form. The method seeks to minimize the integral of the square of the curvature for the approximating spline.

A study of improved algorithms for non-linear regression modeling was initiated.

Computer Systems Laboratory

Alan M. Demmerle, Chief

Clinical Research, Patient Care, Epidemiology

Computer Support for Flow Cytometry/Electronic Cell Sorters (FC/ECS) (NCI, NIAID). This project, started in FY75, now directly supports seven computer systems for the acquisition, display, and analysis of data from eight FC/ECS instruments in two NIH Institutes and two systems in other government agencies (Centers for Disease Control and Department of the Navy). Two systems use the RT-11 operating system to process data from one user at a time. The other sites use the RSX-11M operating system to support multiple users and tasks simultaneously.

The RSX system when used with a FACS II FC/ECS features an LSI-11/73 microcomputer (satellite) that connects to an 11/24 minicomputer (host) via an interprocessor link. A FC/ECS operator interacts with the satellite for parameter entry and data acquisition, which is performed independently of the host. The host stores, displays, and analyzes the data, and prints or plots the results. This system also features the ability to connect commercially available FC/ECS instruments that include computer systems to the RSX/CSL (host) for purposes of data transfer, storage, and/or analysis. In FY85, CSL installed RSX systems in I, NCI; IIB, NIAID, and MOB, NCI. An enhanced and expanded version of the analysis programs (APR) is under development.

Cardiac Scintillation Probe (CC, NHLBI). This nonimaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. The system can continuously derive parameters such as LV compliance, ejection fraction, filling and ejection rates, and various temporal relationships.

In 1985, the probe continued to be used in intervention studies in the catheterization laboratory, NHLBI, on patients with asymmetric septal hypertrophy and coronary artery disease. A second probe is being evaluated as a tool to monitor the left ventricle performance of patients in the Medical Intensive Care Unit of the Clinical Center.

Nuclear Medicine Computer Systems (CC). CSL has continued consultation and support for imaging systems in the Nuclear Medicine Department to assess their changing needs and to evaluate their increased requirements with a view toward their anticipated growth. This year, a Request for Proposal (RFP) for a new department-wide computer system was released. Proposals were received, and then evaluated on their technical merits. It is anticipated that a contract will be signed this year.

The computer processing requirements for Nuclear Medicine are projected to grow 10- to 30-fold over the next few years due mainly to increases in the number of tomographic studies. The new department system will handle the present requirements and will allow for expansion to accomodate the projected growth. It is anticipated that this system will be a node on the proposed Clinical Center Picture Archival and Communication System.

Medical Intensive Care Unit Patient Monitoring Computer System (CC).Patients in the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system comprising a physiologic monitoring system, a catheterization laboratory system, and a software development system. Capabilities of the system include online data acquisition and analysis, medical recordkeeping, tabular and graphical data display, and feedback control, as required in support of patient care and research protocols.

The state-of-the-art catheterization laboratory system combines flexible computerized physiologic monitoring features, with a high resolution x-ray system with digital subtraction angiography capability. Of primary interest is the utilization of the Medical Intensive Care Unit's computer systems in the study of the etiology and therapy of septic shock.

A nonimaging cardiac probe, previously interfaced to the software development system, provides left ventricular volume data by counting scintillations after the administration of an injected radioisotope. Development of data analysis software, markedly different for this probe than for the one in the NHLBI

catheterization laboratory, was completed this year and a clinical evaluation period was initiated.

A cardiac echocardiographic imaging subsystem was interfaced to the software development system this year, allowing the development of special purpose cardiac image analysis software.

Department of Rehabilitation Medicine Computer System (CC). This project involves the development of computerized instrumentation techniques in collaboration with the Department of Rehabilitation Medicine, NIH Clinical Center. An Automated Biomechanics Laboratory System that provides for the simultaneous measurement of ground reaction forces, electromyograms (electrical activity of the muscles), and body kinematics (the position and angles of the limbs and joints in space and time) was installed in FY84 with a combination of purchased instrumentation and computer hardware and software. Techniques are being implemented to automatically acquire anatomical and physiological information from patients, perform required calculations on the data obtained, and display necessary results to the medical staff. In addition, the computer part of the system allows the medical staff to enter patient and staff data into a data base with computer-generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data.

Automated Management of Critically Ill Patients (CC). This research project initiated in FY82 is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal is to use computer-based instrumentation to aid in the differential diagnosis of disease states and the implementation of therapeutic modalities through automated technology.

A state variable approach is used in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Empirical clinical data and realtime monitored values are utilized in model validation. Current project focus is on cardiovascular disorders that give rise to low output syndrome. Software that models the drug administration protocol and the three major subsystems accounting for drug action on cardiovascular function was completed during FY85. An instability previously identified in the cardiovascular dynamics model was eliminated. Newly-derived analytic expressions for the system forcing functions have been incorporated into the cardiovascular dynamics subsystem.

Computer Interfaces for Clinical Laboratory Instruments (CC). CSL designs and implements microprocessor-based systems to aid in automating functions in the Clinical Pathology Department, CC. In previous years, systems were developed for automated cell counters, the entry of hematology morphology data, and hematology white cell differential counting.

This year, an online entry system for urinalysis data was designed, tested, and implemented in the Urinalysis Section of the Clinical Chemistry Service. The system was designed using an IBM PC-XT as the basic workstation. Each workstation allows data to be entered, corrected, and stored. Data are stored on two workstations for redundancy. The two are linked together by an Ethernet Local Area Network. When data entry is complete and data are certified by urinalysis technicians, the system transmits the data to the Hospital's Honeywell 716 computer. New instruments to automatically analyze urine are under development by outside vendors and will be interfaced to this system in FY86 when they become available.

Anesthesia Computer System (CC). This project is a collaborative effort between CSL and the Anesthesiology Service, CC, to develop improved computer-based instrumentation techniques and to identify and investigate ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring, effective and dynamic display formats, intelligent alarm schemes, simple user interface, and automated recordkeeping in the operating room. An additional priority is the increased use of noninvasive monitoring methods.

This year we began implementing our preliminary system design. A graphics package was developed to enable realtime graphic and alphanumeric display. Software was developed to allow serial data acquisition from the front-end patient monitors already in use. In conjunction with a graphic artist, various display

alternatives were designed, presented on our color video display, and evaluated. Methods and devices were evaluated to facilitate physician interaction with this system.

Medical Information Technology Project. This project involves the application of microprocessor technology and improved man-machine interface methods to permit physicians and their associates to communicate more directly with computer record systems. The goal is to develop better ways to automate the essential physician contribution to the health care record that is used in both research and patient care. The methodology focuses on providing disease-specific and problem-specific protocols to lead the user through a tree-structured hierarchy of relevant diagnoses, treatment, tests, and procedures. In past years, a system was developed on a multiuser microcomputer to produce pharmacy prescriptions and patient information based on physician selection. This year, the system was converted for use on a personal computer and additional software modules were added so that it now aids the physician by producing machine-generated patient information and treatment schedules, pharmacy prescriptions, and medical and surgical procedure reports. A local area network was developed to link together several PCs for clinics or practices needing more than one workstation. Pilot studies, under way for four years with a dermatologist, were expanded to include a gastroenterologist. A prototype drug formulary update program was developed to let the physician-user add, delete, or modify drug prescription data.

Cardiac Ultrasound Image Processing (CC). This project, which was initiated during FY84, is directed towards providing the NIH Clinical Center Medical Intensive Care Unit with the ability to assess cardiac function via computer analysis of ultrasound images of the heart.

During FY85, software has been developed for an interactive image processing system to provide an estimation of left ventricular ejection fraction. A hardware/software link has been implemented between the cardiac ultrasound system and a remote computer. Applications programs written by CSL are being evaluated currently.

Automatic Coronary Venous Flow Measurements (NHLBI). An automated system, based on an IBM PC-XT, was developed to measure coronary venous blood flow during cardiac catheterization. Flow is determined by a thermodilution technique using a Baim Coronary Sinus Flow Thermal Dilution Catheter. The goal of this project was to develop a computer system to automatically measure temperature change and calculate coronary venous blood flow, thereby improving the speed and accuracy with which repetitive flow determinations can be made. This system, begun in FY84, was completed early this year and is now routinely used in the Cath Lab to determine coronary venous blood flow.

Speech Analysis System (NINCDS). CSL is assisting the Communicative Disorders Program (CDP), NINCDS, to implement a computer system for acquiring and analyzing speech and motor signals from patients with speech impairments. In FY84, CDP identified a software package called MITSYN that can perform all required functions, and CSL specified a compatible computer system (an LSI-11/73 running RSX-11M PLUS) with analog I/O peripherals.

The computer system was installed in March 1985, and MITSYN was installed in April. CSL is writing the signal acquisition/playback software required to interface MITSYN with the analog I/O devices, and is designing a special buffering device that will enable analog I/O at 50,000 samples/second under the RSX-11M PLUS operating system. The system will be completed at the end of this fiscal year.

Brain Image Registration (CC). An elusive problem faces researchers involved in the correlation of brain form (structure), and brain function (metabolism). Structure is deduced from x-ray computed tomography (CT) images, while metabolism is deduced from positron emission tomography (PET) images. The difficulty concerns the superposition and registration of the tomographic views obtained from these two imaging modalities.

A project team, consisting of staff from CC, NIAAA, and DRS, as well as DCRT, was assembled in early FY85 and is approaching this problem via a two-stage solution. First, we are developing a practical method for the accurate and reproducable placement of the head within a tomographic scanner's aperture, relative to the geometric center of the aperture. Second, we are developing a simplified algorithm for the scaling and registration of digitized images from different scanners. This algorithm is based on the accurate calibration and analysis of the translation between the geometric center of the scanner's aperture and the optical center of the scanner's image plane, as well as interscanner differences in the number of image pixels per centimeter of object space, in the vertical and horizontal axes.

Laboratory Investigation

Molecular Modeling and Sequence Analysis (NIADDK, NCI, Rockefeller University, Boston University). The sequence of some regular proteins, when correlated with other structural information, such as data from x-ray diffraction, fiber diffraction, electron microscopy, and spectroscopic analysis, can be used to evaluate models of protein or polymer structure. Four current studies involve the sequence analysis of keratin and other intermediate filaments (with NIADDK, NCI); computer simulations of the effects of staining for helical proteins such as actin, actin with S1 subunits, and microtubules (with NIADDK); sequence analysis of streptococcal M5 protein (with Rockefeller University); and computer models of branched polymers (with PSL, DCRT).

Image Analysis of Chemical and Biochemical Systems (NIADDK, DRS, NCI, NICHD, Brookhaven National Laboratories). CSL is active on several projects aimed at the processing and analysis of chemical, biochemical, and biomedical images.

- Virus Structure
  Two new virus structures have been studied using image processing techniques developed in this laboratory. The high resolution structure of the herpes simplex virus has been determined (with NIADDK and USUHS). In addition, tail fibers of bacteriophage T7 have been analyzed (with NIADDK, NCI, and Brookhaven National Laboratory). These analyses have been successful in part as a result of new software that has been developed for correlation averaging of single particles (with BEIB and NIADDK).
- Electron Microscopy
  This project facilitates structure determination from electron microscopy. Suitable software, hardware, and scientific expertise has been provided to allow other scientists, primarily at NIH, to use image processing and computer reconstruction to determine or understand a specimen's structure.
- Gel Electrophoresis
  The goal of this project is to allow NIH scientists to easily and accurately quantitate one- and two-dimensional gels. New software has been developed to utilize the features of the new image processing facility and to more easily and quickly analyze gels, autoradiographs, and data from hybridization experiments.
- Cataract Quantitation
  Images produced by the Scheimpflug principle are being used to quantitate eye opacities in a pilot study, whose purpose is to evaluate the potential for the accurate evaluation of changes in cataract patients. This may provide a means of documenting and monitoring cataracts in vivo, allowing clinical trials of drugs that may prevent or reverse the cataract formation process.

Distributed Laboratory Data Acquisition and Control System (DLDACS) (NIADDK). A DLDACS has been implemented for NIADDK in NIH Building 2. The system consists of a network of remote microcomputers connected in a star configuration through a communications processor to a central processing computer. The remote microcomputers handle all of the realtime data acquisition requirements and provide instrument control functions when required. The collected data is normalized, buffered, and transmitted as files over a serial line, using a standard block protocol, to the communications processor. The communications processor serves as a store and forward front end for the central computer. Currently

there are 10 remote microcomputers in the system supporting 12 instruments.

Processing software provided at the host allows LDACS data files to be: added, subtracted, averaged, smoothed, baseline corrected, integrated, differentiated, multiplied by a constant, and added to a constant. The results may be displayed graphically on a Tektronix compatible terminal, typed on a terminal, printed on a line printer, plotted on an X-Y plotter, or transmitted to the NIH DECsystem-10 for additional processing. The development of these programs, started in earlier fiscal years, was completed in FY85. Also in FY85, an additional LDACS interfaced to a Raman spectrometer was added to the system.

Personal Computers in Laboratory Application (DCRT). CSL, in anticipation of widespread use of personal computers in NIH laboratories, has set up a project team to support laboratory applications of PCs. Traditionally, CSL either has collaborated with, or has provided support to, investigators whose research required the use of computers in laboratory or clinical situations.

In the case of personal computer applications, members of the CSL project team will offer advice on system configuration, suitable laboratory software packages for particular applications, and hardware interfacing equipment and techniques. When appropriate, they will suggest alternative, more suitable approaches to a problem.

A major function of this project will be to try to characterize applications as they come to CSL's attention, to develop consistent approaches to these applications, and to develop solutions for commonly encountered problems that cannot be solved with commercial products. This project is a supplement to, not a duplicate of services available through, the DCRT Personal Workstation Office.

X-ray Diffraction Studies of Muscle Tissue (NIADDK). The Computer Systems Laboratory assisted the Laboratory of Physical Biology, NIADDK, in interfacing a computer system to a two-dimensional x-ray detector that is used for x-ray diffraction studies of muscle tissue. The computer system is a MASSCOMP 500 series, which is based on the Motorola 68000 microprocessor and runs the UNIX operating system. The computer was installed in July 1983, and CSL completed the data acquisition software and hardware during FY84. A working x-ray detector was delivered by a contractor in December 1985, and checked out in conjunction with the CSL-developed hardware and software. The system is now in use. There are no plans for further CSL development on this project.

Using the DAOS Realtime Control Language for Retina Research (NIADDK). Laboratory studies of retina electrophysiology and biochemistry performed in LCP, NIADDK, require a computer-based system for high-speed transient data capture and data analysis. CSL provided a microcomputer (LDACS) programmed to acquire data from sources selectable with a patch panel. Although somewhat flexible, the fixed nature of the program limited its adaptability to changing experimental protocols. To meet the need for frequently changing protocols, in FY84, CSL purchased the Data Acquisition Operating System (DAOS) written by Laboratory Software Associates of Melbourne, Australia.

DAOS is an interpreted realtime control language that supports timing functions, virtual data storage and a variety of data acquisition modules. DAOS is extensible by incorporating user-developed software. In FY85, CSL developed software and hardware for computer control of stepping motors to vary experimental conditions and to implement more complex timing sequences. Software is being written to reorganize the DAOS data files to be compatible with the NIADDK computer facility. The value of the DAOS to the laboratory investigator is in the rapidity with which realtime programs may be written and changed.

Advanced Laboratory Workstation (DCRT). The Computer Systems Laboratory started, in late FY85, to develop an Advanced Laboratory Workstation (ALW), which is a small- to mid-size (,000- ,000), 32-bit, UNIX-based computing engine intended for biomedical research laboratory applications. The project involves the development and integration of a wide variety of software packages into a foundation that can be used

by CSL engineers, or scientists themselves, to quickly customize an ALW for a particular purpose.

We plan to include functions that are valuable in the research laboratory and that state-of-the-art technology makes economically feasible: data acquisition, scientific data processing, data presentation, networking, data base management, modeling, document preparation, and software development. Our strategy is to purchase the best software that is compatible with the workstation hardware and operating system and integrate it under a user-friendly desktop interface. Modern programming techniques such as object-oriented programming will be explored as a means of increasing productivity and software portability.

Program Management And Administration

Library Automation (DRS). Since FY79, CSL has provided technical consultation to the NIH Library. As automation has proceeded in the library, CSL has provided a requirements study, a market survey, a cost-benefit analysis, programming assistance, and technical support in contract negotiation. As the introduction of microcomputer technology made more extensive library automation cost effective, CSL has extended its technical support to the smaller DCRT Library.

As a result of CSL efforts, the NIH Library has purchased a turnkey library system that will support an online catalog and automated control of circulation, acquisitions, and serials.

In FY85, our technical support of the NIH Library Automation project ended. The NIH Library's system is operational as an automated catalog and a circulation control system. The turnkey vendor is committed to installing both an acquisitions and a serials control system. CSL has provided limited consultation to both the NIH Library and the DCRT Library in the utilization of personal computers and networking technology.

Integrated Communication System (NIA). In FY85, CSL made a study of the automation opportunities in the NIA offices. Special attention was paid to the flow of information between disparate offfices in the Institute and a preliminary investigation was made of the interface to the Grants Program data bases on NIH's IBM System 370. The written report of this study, which has been accepted and adopted by NIA, recommended that NIA develop a network of personal computers.

It is expected that future goals of the projects will include the investigation of additional areas of office automation and assistance in the implementation of the NIA network. It is hoped that a generalization of this type of network solution will be adaptable to widespread use at NIH.

Job Tracking and Control System for the Medical Arts and Photography Branch (DRS).

Besieged by an ever increasing volume of files, forms, and a need for information retrieval, the Medical Arts and Photography Branch, DRS, requested that CSL develop a job tracking and control system. In addition to the need for a staged implementation of job tracking, other prominent requirements included: high reliability, expandibility, and archiving capability for multicopy forms, a capability of performing administrative queries, a word processing capability, and ultimately a local billing capability. During late FY85, CSL analyzed the operational requirements and designed a system involving a network of IBM personal computers. The first phase, which includes five IBM PC-XT's and one IBM PC-AT connected via a 3COM Ethernet, is being implemented during FY85.

Biomedical Communications and Conference Support

Computers in Cardiology Conference. CSL continued its support of the annual International Conference on Computers in Cardiology. This year the conference will be held in Linkoping, Sweden. The Conference provides a forum for direct interaction and exchange between physicians, computer scientists, and engineers who are involved in various aspects of clinical computer systems in the field of cardiology.

CSL Consulting

This year, as in past years, CSL provided consultative assistance to several intramural and extramural program areas.

- CSL assisted DRS in monitoring contractor performance on the development of the Veterinary Research Branch Animal Data Management System for which CSL previously prepared the RFP.
- A CSL staff member served the second year of a two-year term on a standing committee for evaluation of NCI intramural support contracting.
- CSL helped the Medical Neurology Branch, NINCDS, to select a computer data acquisition system for their Magnetoencephalography Program.
- A CSL staff member participated in a peer review of the NIEHS Computer Technology Branch.
- A CSL staff member evaluated the performance of the microcomputer-based programmable data acquisition terminals used to acquire animal test data for the National Toxicology Program by observing the use of the terminals at two contract laboratory sites: Litton Bionetics and Batelle Memorial Institute.
- Technical consultation on the DEC RSX-11M operating system was provided to ten investigators representing five NIH Institutes and two organizations outside NIH.
- Services are provided for Flow Cytometer/Electronic Cell Sorting (FC/ECS) sites. CSL continued to provide technical assistance and guidance for an FC/ECS computer system at the Uniformed Services University of the Health Sciences. CSL consulted with Naval Medical Research Institute of the National Naval Medical Research Center to convert their system from RT-11 to RSX.

Computer Research And Technique Development

Medical Image Data Compression (DCRT). This project involves reducing the number of information carrying units used to represent a medical image, in order to improve the efficiency of transmission and storage of such images. Various image data compression techniques and their application to medical images are being evaluated with regard to the amount of compression attained and the quality of the reconstructed image. Methods for implementing these techniques that will be suitable to the clinical environment have been investigated.

During FY85, Hadamard transform coding techniques were combined with noise-free Huffman encoding methods to yield an aggregate compression, based on four images, ranging from 10:1 to 15:1 with good image fidelity.

Integrated Input/Output (DCRT). The Integrated Input/Output project is an attempt to expand the user interface of a personal computer from the usual keyboard input and CRT display to include more friendly and efficient modalities of communication. CSL efforts on this project include the development and modification of hardware and software to support desirable interface features like speech recognition and voice response, bar code interpretation, touch-sensitive CRT screens, and graphics input devices. This year a demonstration system incorporating keyboard, touch screen, barcode, mouse, and voice recognition inputs, was developed to show the feasibiltiy and flexibility of letting a user choose the input that fits this situation. Methods also were developed to let a DCRT/DMB programmer who is a quadriplegic operate and program his own personal workstation by voice command.

DCRT Local Area Network (LAN) (DCRT). In recognition of the increasing importance of local area networks (LAN's) in laboratories, hospitals, computer facilities, and offices, CSL is planning a network for DCRT. Two goals led CSL to undertake this project. First, we thought it important to develop expertise in LAN technology so that we will be able to offer competent advice to other NIH organizations in the future. Second, DCRT has some 40 IBM PC's, plus numerous other terminals, modems, and computer systems that can benefit from interconnection by an LAN.

We selected the Ethernet LAN because it is an established standard, supported by products from a broad spectrum of companies. In FY84, we planned the

Ethernet for all of DCRT and installed it in Building 12A. This year, we extended it to Buildings 12 and 12B. The network now spans 1,250 meters of cable and interconnects 45 IBM PCs and five host computers.

Expert Systems in Medicine (CC). A new initiative this year concerns the development of "expert systems" in the medical environment. Expert systems are present-day, feasible applications of artificial intelligence techniques. They are knowledge-based, in that they contain knowledge contributed by experts, and organized, together with a set of rules for applying the knowledge, by "knowledge engineers." Generally, they function best in specific narrowly defined, yet still complex, problem areas.

Likely medical areas for the application of expert systems include physical diagnosis, therapy planning, and clinical data interpretation. An initial objective for the project is to develop, in collaboration with the Critical Care Medicine Department of the Clinical Center, an Intravenous Chemotherapy Advisor Expert System for use in an intensive care unit. The specific problem of interest is drug therapy to stabilize cardiodynamic function. Longer range objectives include: the investigation of languages for implementation for expert systems, development of techniques for this relatively new field, and application of expert systems technology to other appropriate areas such as office automation.

NIH Campus Area Network. The goal of this project, which was started in FY85, is to provide NIH with an assessment of networking requirements on a campus-wide basis, to study available technology, and to recommend appropriate designs to meet the requirements. We expect to find applications ranging from video data transmission including images and graphics, to mainframe/microcomputer interconnection, to interconnection among individual local area networks.

Research Projects

Computer Support for Flow Cytometry/Electronic Cell Sorting (FC/ECS)

Principal Investigator: R. Fico (DCRT/CSL). Also L.K. Barden, W. Gandler (DCRT/CSL); S.O. Sharrow, D.A. Stephany (NCI/I).

This project provides computer support for two Coulter MDADS, one Becton-Dickinson (B-D) FACS IV and four B-D FACS II FC/ECS instruments. High sample throughput, from data acquisition to data display and analysis, is the principal system feature. Currently, there are two versions of data acquisition and analysis systems developed and supported by CSL for the Cell Sorter Community at NIH. One version uses a single computer that runs under the RT-11 operating system. Another version, referred to as the RSX system, uses at least two computers.

A host computer, a Digital Equipment Corporation (DEC) 11/24, is used to analyze and store data. One or more satellite computers acquire data from the instrument and are connected to the host through a hardware link. The RSX system features include data acquisition, data analysis, and recordkeeping utilities within a multiuser/multitasking environment. RSX systems were installed in FY84 at the Immunology Branch (I), NCI; the Immunobiology and Immunochemistry Branch (IIB), NIAID; and the Centers for Disease Control, Atlanta, Georgia. In first quarter of FY85, a second satellite was installed at IIB, NIAID, and in the second quarter of FY85, CSL converted an older RT-11 system at the Medical Oncology Branch (MOB), NCI, to the RSX system.

*Background and Objectives:*Since FY75 CSL has provided engineering, system integration, and software support necessary to meet the data acquisition, data display, and analysis needs of several investigators using FC/ECS instruments at NIH. Software development and testing is done on a DEC PDP-11/24 computer system owned by CSL. This allows investigators to have full use of their systems while new software is being developed.

Both the RT-11 and RSX systems allow data collection of multiple parameters on individual cells. Typically these are forward and side light scatter at various fluorescence frequencies. The data can be collected in single parameter or correlated dual parameter modes.

Data analysis and display programs allow the experimenter to produce various statistics and hardcopy displays from the acquired data. These programs include two-dimensional analysis, three-dimensional hidden line display, contour maps, and vertical slice sections. Also included are cell cycle analysis programs used for DNA analysis.

Progress in FY85: Major efforts in FY85 included hardware/software installations and continued software development for the RSX system. The RSX system was developed for I, NCI, in order to provide support of current and anticipated workloads including sophisticated data acquisition and recordkeeping functions. This system is available to other NIH FC/ECS sites as required.

The data acquisition system consists of a PDP-11 host computer running RSX-11M and one or more satellites connected to the host. Data acquired by a satellite is sent over a link and stored at the host.

The development of the link software for the NIH-designed LSI-11 satellite was completed in FY82. The RSX satellite collects up to four single parameters simultaneously with one correlated dual parameter pair, or it can collect up to two simultaneous correlated dual parameter pairs. A feature called auto-acquisition allows the operator to prescribe acquisition parameters independent of acquisition. The parameters are stored in a file and recalled at the time of acquisition, thereby saving the operator the tedium of entry during acquisition. Currently, there are two such satellites. One of these was installed in FY85.

In the first quarter of FY85, additions were made to the CONVERT conversion utility. This is an open-ended software effort designed to accomodate old and new file formats. CONVERT translates various types of data files to the RSX format. To date, this utility handles all older RT/CSL forms and FACS 440 RT-11 based files.

CSL developed software and hardware to connect Coulter's Multi-Data Acquisition and Display (MDADS) computer to the RSX host via the MDADS high-speed parallel port. The MDADS collects data from Coulter's EPICS V flow cytometer and stores the data as files on the MDADS disk media. Subsequently, these files are transferred to the RSX host where they are converted to the RSX/CSL data format, stored, and analyzed. The first MDADS/RSX connection occurred in FY84 at IIB, NIAID, and a second took place in FY85 at the MOB, NCI.

Improvements in disk drive technology prompted CSL to update the RSX system and data storage disk devices. In the third quarter of FY85, CSL acquired the 80Mb CDC9710 removable Winchester and 160Mb CDC9715 fixed Winchester disk drives. These drives offer a reduction in physical space required to store data by a factor of fifty, and a reduction in cost per unit storage by a factor of sixteen over the previously used drives. During the fourth quarter of FY85, a second set of drives were installed at the I, NCI site.

A new analysis package, APR, was added to the RSX system. APR was adapted from CSL's Distributed Laboratory and Data Acquisition and Computer System (DLDACS) project to CSL's Flow Cytometry project by including flow cytometry specific application software. By the third quarter of FY85, it was modified to encompass all of the existing two-dimensional analysis program capabilities and extends these through its extensive command set. APR is not specific to the obsolete Tektronix 4025 terminal as are the existing FC/ECS analysis programs. Instead, APR adapts to different terminals and includes the standard graphics calls associated with the popular Tektronix 4010 series terminals.

The design of a new CSL flow cytometry interface was completed in the third quarter of FY85 and fabrication of the interface began in the fourth quarter. This interface collects eight simultaneous parameters and is expandable to sixteen.

CSL has responded to external requests and has provided copies of its software and documentation to FC/ECS sites in the U.S., Australia, and Europe.

Proposed Course: In the forthcoming year, CSL plans to continue development of the RSX system for both analysis and acquisition. Adaptation of APR to handle three-dimensional capability, commensurate with the SLICE, CONTOR, and DSP3 programs, has already begun and will continue in FY86. It is expected that

CSL will complete the new interface sometime in FY86 and modifications to the current data acquisition program to adopt this interface will follow. Consultation to the Naval Medical Research Institute (NMRI) of the National Naval Medical Research Center (NNMRC) for conversion of the old RT-11 system to the new RSX system began in FY85 and CSL is expected to complete this conversion for NMRI in FY86. Plans to connect a Becton-Dickinson FACS IV and FACS Analyzer/Consort-30 to the 11/24 have already begun and the development will continue into FY86. CSL will continue to maintain the RT-11 and RSX-based FC/ECS sites at NIH.

Cardiac Scintillation Probe

Principal Investigator: H.G. Ostrow (DCRT/CSL). *Also:* S. Bachrach, M. Green (CC/NM); R. Bonow, D. Rosen, S. Betocchi (NHLBI/CB).

CSL has continued the development of its Cardiac Scintillation Probe System begun in 1977. The cardiac scintillation probe is a transportable device used to noninvasively monitor left ventricular function. The system uses nuclear medicine ECG-gated scintigraphic techniques and consists of a small detector and microcomputer system mounted on a cart.

This nonimaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catherization, permits simultaneous quantification of the variation of LV volume and pressure. By simultaneously measuring LV volume and LV pressure, parameters such as LV compliance can be continuously monitored, in addition to such measurements as ejection fraction, filling and ejection rates, and temporal relationships.

This year the probe continued to be used for intervention type studies in the NHLBI catheterization laboratory. The probe also is being evaluated as a tool to monitor the left ventricle performance of patients in the Medical Intensive Care Unit. Development is continuing on increasing the detection efficiency of the probe and in quantifying the limitation of the technique.

Background and Objectives: The development of the cardiac scintillation probe is a continuation of CSL's collaboration with the Nuclear Medicine Department, CC, and the Cardiology Branch, NHLBI. In 1977 CSL began the development of a cardiac scintillation probe system, using a small NaI detector and microcomputer system. This system produces a time activity curve (LV volume curve) that can be used to calculate various parameters of cardiac function such as ejection fraction, peak ejection rate, peak filling rate, and temporal relationships. The system is easily transportable and allows continuous monitoring of cardiac function at the bedside or other locations in the Clinical Center outside the Nuclear Medicine Department.

Methods: The system consists of a three-inch diameter NaI scintillation probe, probe electronics, microcomputer system, and display. The system is programmed to acquire scintillation data, to process the data, and to plot and display various parameters of left ventricular (LV) function. In the catheterization laboratory, pressure-volume measurements are used to study the effects of drugs on patients with various heart diseases.

*Progress in FY85:*This year the probe continued to be used in the catheterization laboratory on several intervention protocols to determine the effect on left ventricular function. The data acquisition and most of the processing is now being performed by personnel from the Nuclear Medicine Department and Cardiology Branch. A Hewlett-Packard computer system to replace the Intel microcomputer system was received this year. The Hewlett-Packard computer will accomodate new requirements for the probe system and will be compatible with the existing analysis software available in the Nuclear Medicine Department.

The application of the probe in the Medical Intensive Care Unit, CC, continues to be investigated.

*Significance to Biomedical Research:*Nuclear Medicine techniques provide a relatively noninvasive procedure to assess left ventricular function. The cardiac scintillation probe permits this capability to be used for clinical research studies at the bedside and in the catheterization laboratory. The pressure-volume relationship produced by the probe system allows the effects of drugs to be quantitated.

Proposed Course: Development activities in response to new applications are expected to continue. The delay in acquiring the Hewlett-Packard computer system postponed the effort to make the probe and camera systems more compatible. Making the system compatible to the extent possible will reduce the resources required to support the probe system and will allow new capabilities developed for the camera systems to be implemented quickly on the probe system.

Medical Intensive Care Unit Patient Monitoring Computer System

Principal Investigator: K.M. Kempner (DCRT/CSL). Also: J.E. Parillo, S.L. Huntley (CC/CCM); L.W. Freeman (DCRT/CSL); J.P. Fessler (DRS/BEIB).

The dynamic events occurring within the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system. Capabilities of the system include online data acquisition and analysis, medical recordkeeping, tabular and graphical data displays, and feedback control, as required in support of patient care and research protocols. Elements include a minicomputer-based Patient Data Management Subsystem, a Software Development Subsystem, and a state-of-the-art catheterization laboratory that includes a flexible computerized Vascular Research Subsystem, with physiologic waveform processing features, and a high resolution x-ray system with digital subtraction angiography capability.

Of primary interest is the utilization of the Medical Intensive Care Unit's computer systems in the study of the etiology and therapy of septic shock.

*Background and Objectives:*The Medical Intensive Care Unit (MICU), administered by the Department of Critical Care Medicine in the NIH Clinical Center, receives critically ill patients from clinical programs of NIH. The MICU comprises a five-bed ward area, a pair of isolation beds, and a vascular research laboratory. The research goals of this unit include the development of techniques for automated patient monitoring and noninvasive measurements of the cardiovascular and respiratory systems. In addition, catheterization studies are performed as necessary to obtain data that are available only through invasive methodology.

Working with Clinical Center staff, CSL contributed to the engineering design of the intensive care unit. CSL also undertook the specification, procurement, and installation of the bedside patient monitoring equipment and the six computer systems:

1. a Patient Data Management System used for automatically monitoring patient variables, manually entering patient data, retrieving information online, and keeping medical records;
2. a Vascular Research Subsystem used for acquiring and processing cardiovascular pressure waveforms, measuring cardiac output, displaying measured results online, and generating a cardiac catheterization report;
3. a Software Development Subsystem used for developing software for the above described systems, as well as nuclear medicine and cardiac ultrasound studies;
4. an Ultrasound Imaging Subsystem used to allow the visualization of intracardiac structures via multiformat displays and to facilitate the detection of structural abnormalities and other cardiac defects;
5. a Pulmonary Function Testing Subsystem used to calculate parameters such as vital capacity and lung volumes, and to generate flow-volume loops; and
6. a data analysis and graphics subsystem used to correlate data obtained from the other computerized subsystems, as well as immunology and clinical pathology laboratory data.

The first four systems were purchased from the Hewlett-Packard Corporation and all use identical minicomputers. The Collins Corporation designed and manufactured the microcomputer-controlled Pulmonary Function Testing Subsystem. An IBM personal computer (PC-XT) and plotter form the basis of the data analysis and graphics subsystem.

Major Findings: The automation of the MICU has aided the medical staff by managing the large amount of data needed for the care of the critically ill patient, performing desired calculations, and allowing measurements that would not otherwise be possible.

Progress in FY85: A nonimaging cardiac probe previously interfaced to the software development system provides left ventricular volume data by counting gamma ray-induced scintillations, after the administration of an injected radioisotope. Data analysis software development was completed this year, and a clinical evaluation period was initiated.

The cardiac ultrasound imaging subsystem's interface to the software development subsystem allowed the implementation of experimental algorithms for the processing of cardiac ultrasound images.

Proposed Course: Future efforts will center on hardware and software modifications necessary to enhance the system's ability to support patient care and research protocols. Possible modifications to the primary Patient Data Management Subsystem include the addition of urine output measurement scales and the computerization of fluid infusion therapy utilizing existing microprocessor-controlled infusion pumps.

Rehabilitation Medicine Department Computer System

Principal Investigator: R. L. Martino (DCRT/CSL). *Also:* M.O. Jarret, G.C. Hunt, A. Novick, W. Schneiderwind, N.L. Gerber (CC/RM); D.C. Carpenter, J.E. Sullivan (DCRT/CSL).

This project involves the development of computer techniques in collaboration with the Department of Rehabilitation Medicine of the NIH Clinical Center. Techniques are being implemented to automatically acquire anatomical and physiological information from patients, perform required calculations on the data obtained, and display necessary results to the medical staff.

An Automated Biomechanics Laboratory System that provides for the simultaneous measurements of ground reaction forces, electromyograms (electrical activity of the muscles), and body kinematics (the position and angles of the limbs and joints in space and time) has been installed with a combination of purchased instrumentation and computer hardware and software. The computer part of the system also allows the medical staff to enter patient and staff data into a data base with computer generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data.

In FY85, the system was placed in clinical operation while activities continued with the development of laboratory instrumentation and the enhancement of the computer system that supports the laboratory's functions.

Background and Objectives: The Department of Rehabilitation Medicine provides physiatric evaluation and treatment, physical therapy, occupational therapy, and speech therapy for NIH Clinical Center patients referred by NIH physicians. This department supports the efforts of, and collaborates with, physicians engaged in research relevant to physical rehabilitation medicine. It also initiates both clinical and basic research independent of the Institutes in the rehabilitation of mentally and physically handicapped individuals.

In support of these goals, CSL is developing the Automated Biomechanics Laboratory System that provides methods for the quantitative analysis of human motion. The instrumentation includes five motion cameras with infrared light sources that are used to acquire the spatial coordinates of anatomical points on the patient's body with reflective markers, two force platforms that are used to measure patient ground reaction forces, and hardwired and telemetry electromyogram acquisition hardware that is used to measure patient muscle activity. This instrumentation is connected to a computer system that performs the necessary data acquisition, calibrations, processing, display, and storage functions.

Progress in FY85: During the past year, the Automated Biomechanics Laboratory System was placed in clinical operation. The medical staff learned to use the system and experimented with various camera and reflective marker configurations in order to determine the optimal configurations for their required clinical applications. The following is a brief description of the medical projects that were initiated in FY85:

1. Three-Dimensional Analysis of Tibia Vara and Calcaneal Eversion in Static and Dynamic Conditions of Stance. The Department of Rehabilitation

Medicine is developing measurements that accurately reflect the interrelationship between tibia varia and calcaneal eversion to assess the stresses placed upon the foot and lower limb during gait, and will use these results to determine the proper therapeutic intervention for patients with lower limb problems.
2. Leg/Hindfoot Orthosis as a Treatment for Hindfoot Pain. The Department of Rehabilitation Medicine is evaluating the effect a modified ankle/foot orthosis has on general gait parameters, ankle and knee motion, and the forces generated at the ankle and knee joints with patients that have hindfoot pain.
3. Postural Mechanisms in Neurologic Diseases. The National Institute of Neurological and Communicative Disorders and Stroke is studying the physiology of postural disturbances in patients with neurologic disorders. Initially, measurements are being made on patients that have Parkinson's Disease.

Also during the past year, work continued on the development of the instrumentation and computer system that supports the laboratory's functions. This included the installation of a four-channel electromyogram telemetry system. An Analog Signal Acquisition Subsystem, which is used to acquire and filter the analog signals such as the electromyograms and force platform outputs in the laboratory, was designed and installed.

A Biomechanics Graphics Software Package was purchased in order to give the medical staff flexibility in the graphical display of the biomechanical data that is obtained with the system. Three high resolution graphics terminals, which can be used with the laboratory's existing software as well as the new graphics package, were selected and purchased. A new multipen plotter that was obtained this past year will provide publication quality hardcopy of the generated graphical output.

A major enhancement to the computer system was the addition of a PDP-11/73 computer as a front-end processor to the already existing VAX-11/750. The PDP-11/73 will be used to acquire and process the data obtained from the laboratory instrumentation, and will transmit the processed data to the VAX-11/750. The VAX-11/750 will be used for analysis, graphics, storage, and report generation functions.

The Automated Biomechanics Laboratory System is presently located in a temporary site on the first floor of the Clinical Center. The construction of the final location of the laboratory was initiated on the sixth floor of the Clinical Center. The mounting structure for the force platforms that will be installed in the new location was designed and ordered.

The collaboration with the Gait Analysis Laboratory, Department of Orthopedic Surgery, Children's Hospital Medical Center, and Harvard Medical School continued. In the future, computer programs, patient data, and engineering and medical expertise will be exchanged with this group.

Significance to Biomedical Research: The computer system will be used to evaluate the effectiveness of drug therapy, orthotic and prosthetic devices, and medical interventions on patients who are amputees, or have arthritic, orthopedic, and neurological conditions. It will also be used as a teaching tool to help these patients learn to function with their disability in an efficient manner. Many medical centers in the United States, Great Britain, Europe, and Japan are presently establishing automated biomechanics and gait analysis laboratories. Therefore, any new developments made on this project will benefit users of these automated systems, as well as patient care and clinical research within the Department of Rehabilitation Medicine at NIH.

Proposed Course: During the coming year, the mechanics of motion of amputees and the impact of prosthetic design on gait characteristics will be evaluated in addition to the clinical projects already in progress. Also, the effects that shoe orthoses and hand splints may have for contiguous joints of the upper and lower extremities in arthritics will be studied.

When the final laboratory location is completed, the instrumentation computer system will be moved from the temporary site. Many additions will be made to the system in the future including the selection and integration of visual cameras and video recorders, including the electronics needed for synchronization

with the motion cameras; the implementation of energy expenditure calculation software; the addition of a statistical analysis software package; and the development of methods for accurately determining the velocity and acceleration of anatomical points from acquired motion data, including consideration of the required camera resolution and frame rate and digital differentiation techniques.

Automated Management of Critically Ill Patients

Principal Investigator: K.M. Kempner (DCRT/CSL). *Also:* J.E. Parrillo (CC/CCMD); N. DeClaris (Univ. of MD).

This research project is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal is the utilization of computer-based instrumentation to aid in the differential diagnosis of disease states and the implementation of therapeutic modalities through automated technology.

A state variable approach is utilized in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Empirical clinical data and realtime monitored values are utilized in model validation. Several alternative methods for closed-loop automated medical interventions are being investigated.

Background and Objectives: Noninvasive diagnostic and therapeutic techniques generally involve the application of sophisticated electronic technology and mathematical modeling techniques to the detection of pathophysiologic states. Particularly interesting and important problems involve cardiovascular disorders that give rise to low output syndrome.

There is no singular cause for this syndrome, and therefore effective therapy requires the differential diagnosis of numerous contributory disturbances in cardiovascular homeostasis. Effective therapy principally involves the administration of one or more fluids and/or drugs in a critical care unit environment.

Methods Employed: In order to accomplish the goal of developing systems capable of assisting in the medical management of a critically ill patient on a closed-loop basis, it will be necessary to develop validated models. Calculated physiologic parameters will be compared to measured physiologic data as the patient's response to the selected therapy progresses.

A mathematical formulation of the relevant subsystems was developed for a patient in a critical care unit setting. This includes the modeling of three principal subsystems: Pharmacokinetics, Drug/Receptor Interactions, and Cardiovascular Dynamics. Progam output includes recommendations for therapy as well as predicted pre- and post-intervention physiologic data values.

A package of FORTRAN programs, which models the drug administration protocol, and the three major subsystems accounting for drug action on cardiovascular function, were implemented on the IBM System 370 facility. These programs simulate the intensive care unit environment and the patient's response to the theoretical chemotherapeutic interventions.

Progress in FY85: An instability previously identified in the cardiovascular dynamics model was eliminated. Newly-derived analytic expressions for the forcing functions of the hemodynamics subsystem were incorporated into the model.

Significance to Biomedical Research: The use of automated systems in the implementation of therapeutic protocols within a critical care unit adds a new treatment modality and will have a major effect on protocol design. It will afford improvements in protocol design for patient care, clinical drug trials, and the study of the etiology and therapy of specific disease entities. In addition, the automation of therapeutic interventions, as proposed, will significantly expand the clinical and research data bases.

Proposed Course: Extensive testing of the software package will begin. Modifications will be incorporated into the models as necessary to improve system performance. Existing critical care protocols will be investigated to identify those components in which automated therapeutic modalities can easily be accommodated within the framework of this research effort. An important aspect to be evaluated is the risk to the patient versus the realizable benefits.

Selected protocols will be implemented utilizing the closed-loop techniques developed in this project, with the objective of carrying out controlled clinical trials and quantitatively evaluating their effectiveness.

Brain Image Registration

Principal Investigator: K. M. Kempner (DCRT/CSL). *Also:* M. V. Green (CC/NM); J. L. Johnson, D. E. Rio (NIAAA/LCS); J. J. Vucich (CC/DR); J. F. Fessler (DRS/BEIB).

An elusive problem faces researchers involved in the correlation of brain form (structure), from x-ray computer tomography (CT) images, and brain function (metabolism), from nuclear medicine positron emission tomography (PET) images. The difficulty concerns the superposition and registration of the tomographic view obtained from these two imaging modalities.

The project team's approach to this problem is based upon a two-stage solution. First, we are developing a practical method for the accurate and reproducible placement of the head within a tomographic scanner's aperture, relative to the geometric center of the aperture. Second, we are developing a simplified algorithm for the scaling and registration of digitized images from different scanners. This algorithm is based on the accurate calibration and analysis of the translation between the geometric center of the scanner's aperture and the center of the scanner's field of view, as well as interscanner differences in the number of image pixels per centimeter of object space, in the vertical and horizontal axes.

*Background and Objectives:*Images derived from CT scanners are typically interpreted as descriptive of the structure of anatomic features in the tissue beds illustrated. Images derived from PET scanners are usually interpreted as descriptive of the sites of metabolism or binding of appropriately labeled, injected or inhaled radiopharmaceutical agents.

In order to assist the correlation of structure and metabolism, it would appear to be useful to allow the precise alignment and superposition of CT and PET images of the same brain section. Images, in digital format, from CT and PET scans of a specific brain section, would be processed and combined at an image display facility remote from the scanner sites.

*Methods Employed:*Precise orientation of the subject's skull within the scanner's aperture will be monitored and recorded through the use of a Polhemus Navigation Systems position/orientation transduction subsystem connected to an IBM PC-XT. The position/orientation measurement subsystem's sensor can be temporarily fixed to an oral appliance, similar to a bite plate, which is molded to match the upper set of teeth. It is expected that this will allow the reproducible placement of the sensor with respect to the subject's skull.

Initial studies will be performed utilizing CT images from one of the Diagnostic Radiology Department's GE 8800/9800 family of x-ray tomographic scanners. Corresponding PET images will be obtained from the Neuro-PET scanner located within the Nuclear Medicine Department. Image processing and display will be performed utilizing the NIAAA imaging system, consisting of a DEC PDP-11/24 minicomputer and a Gould-DeAnza 6400 Image Processor subsystem.

*Progress in FY85:*During this initial project year, the concept for the brain image registration system was devloped and carefully tailored around the design-limiting component, the position/orientation measurement subsystem. Experimental studies were conducted in which the position/orientation measurement subsystem was tested in an operational configuration at the selected CT and PET scanners sites. Preliminary data suggests that satisfactory operation of the position/orientation measurement subsystem can be achieved.

All components necessary to assemble the prototype brain image registration system have been obtained and system fabrication has been initiated. Experimentation with sensor attachment techniques has resulted in the development of an inexpensive custom-molded oral appliance to allow sensor fixation to the subject's skull. Other approaches to the fixation problem are also under investigation.

*Significance to Biomedical Research:*The driving force behind the goal of brain image registration is the need

to develop a greater understanding of the processes underlying the generation of PET images. It is hoped that development of techniques for the accurate correlation of CT structural data with PET metabolic information will enhance this understanding.

*Proposed Course:*After the prototype brain image registration system has been fabricated, software will be developed and integrated into the IBM PC-XT and the DEC PDP-11/24 to perform the necessary skull alignment and image manipulation function distributed between these computer systems. Testing and evaluation of the prototype brain image registration system will then begin.

Urinalysis Data Gathering System

Principal Investigator: J. E. Sullivan (DCRT/CSL). *Also:* D. W. Blank, A. Faust, M. Rawe (CC); P. S. Plexico (DCRT/CSL).

This project involves developing a multiworkstation system for online entry of urinalysis data for the Clinical Pathology Dept., CC. Each workstation is based on an IBM PC-XT and can collect data from interfaced instrumentation as well as from technical personnel directly. Multiple workstations will be able to share data using an Ethernet Local Area Network (ELAN). In addition, each workstation will have a communications link to the Honeywell 716 (H716) clinical laboratory computer. The test results are made available to the health care professionals through the Clinical Center's Medical Information System.

*Background and Objectives:*The development of this system is a continuation of CSL's Computer Interfaces for Clinical Laboratory Instruments. The system will replace a Mark-Document Reader (MDR) used to read urinalysis test results from a card on which technical personnel record them. These results are then transmitted to the H716.

The MDR cannot be interfaced to new instrumentation being developed that can perform various urinalysis tests. The present system requires the data to be sent to the H716 and then certified by comparing a H716 printout with the results on the cards. It was therefore decided to create a new system based on an IBM PC-XT that would allow data to be collected from these new instruments, as well as entered by technical personnel, and certified before sending them to the H716.

By certifying the results before they are sent, time is saved in the certification process, thereby achieving quicker availability of test results to health care professionals. It also was decided to link the workstations together with an ELAN to allow test results to be shared between workstations and to have the data stored redundantly in case a workstation fails.

*Progress in FY85:*The system software was developed on one IBM PC-XT and tested successfully for data entry, data manipulation, local data storage, and communicating the data to the H716. An ELAN was implemented on two workstations to redundantly store the same data. This redundant local storage will prevent the loss of data should a malfunction occur in one of the workstations. Technical information about one of the new instruments being considered for interfacing has been made available. We determined that interfacing this device presents no problem should it be acquired.

*Proposed course:*New analytical instruments for performing urinalysis tests will be interfaced to the system when they are purchased by the CC. Other workstations may be added to the system by being connected to the ELAN. The only limitation to the number of workstations that may be added is the number of available communication lines to the H716. Additional urinalysis tests that are not performed at this time may be incorporated in FY86 as new instrumentation allows new tests to be added.

Anesthesia Computer System

Principal Investigator: P.S. Plexico (DCRT/CSL). *Also:* D. Lees, D. Lawson (CC); L. D. Nadel, R. B. Dew (DCRT/CSL).

The purpose of this project is to develop improved computer-based instrumentation techniques and to identify and investigate ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring, effective and dynamic display formats resulting in rapid interpretation and diagnosis, intelligent

alarm schemes, simple user interface, and automated recordkeeping in the operating room. An additional priority is the increased use of noninvasive monitoring methods.

The primary motivation is improved medical care and patient safety. The use of automated techniques should greatly enhance the anesthesiologist's ability to forsee potential deterioration of the patient's physical condition as well as result in a more accurate patient record. Additionally, the anesthesiologist will be free to spend more time directly observing and caring for the patient and viewing the operation in progress.

Background and Objectives: In the past decade or so, electronic and computer technology has found its way into the operating room primarily through an assortment of discrete patient monitoring devices. These devices have been generally independent of one another, each with its own output display (e.g., oscilloscope, analog meter, printed stripchart, alphanumeric indicators) and set of alarm indicators (e.g., flashing light, electronic beeper, high-pitched tone).

Numerous displays tend to be confusing and divert the anesthesiologist's attention from the patient. Various alarm indications are confusing; a singular, nonintegrated alarm scheme results in a relatively high percentage of false alarms causing the physician to simply disable or ignore alarm warnings. Our aim has been to develop a microcomputer-based, fully integrated display, analysis and reporting system using existing, commercially available patient monitors for front-end patient data acquisition.

Planned key features of the overall system include: (1) single video color display for waveforms, graphics, and alphanumerics, (2) trend accumulation and analysis, (3) intelligent alarm scheme making use of both realtime and trend information, (4) automatic report generation including lab information, results of calculations, and anesthesiologist's notes, and (5) development and use of additional noninvasive monitoring techniques for a more complete assessment of a patient's status.

Progress in FY85: This year we began implementing our preliminary design. The microcomputer system was upgraded from a Micro LSI 11/23-Plus to a Micro PDP 11/73 running the RSX11M-Plus operating system, thus increasing processing speed and task-related memory. Project activities were focused on display development, data acquisition, and user interface.

A Matrox QRGB-GRAPH display module with 512x512x4 resolution is being used for display generation. A Pascal-callable subroutine graphics library was developed to facilitate use of this module for both graphic and alphanumeric display. Vectored alphanumeric generation was used, enabling the use of arbitrary scale factors.

Traditional operating room displays are typically difficult to interpret as the manufacturer tries to cram as much patient information as possible into a single display screen format. The recent introduction of color into these displays generally has resulted in more confusion rather than increased clarity. A graphic artist was consulted in an effort to design more efficient, informative and intelligible data presentations. The attempt is to apply color both meaningfully and aesthetically.

Design and evaluation of both traditional (e.g., realtime waveforms and alphanumerics) and nontraditional (e.g., three-dimensional plots, bar graphs, trend displays) formats was begun. Rather than trying to use only a few dense displays, our approach has been to provide a system of simplified multiple screen formats to be either selected by the anesthesiologist or automatically displayed, depending on the medical situation.

Software was written to control transmission of serial data from both the Spacelabs Vitatek 511 patient monitor and the Critikon Dinamap blood pressure cuff to the Micro-11 computer. Another CSL project has developed a Transaction Synchronization Device (TSD) which, along with an A/D converter (Data Translation #3382), will allow continuous analog data acquisition and conversion with minimal CPU intervention. We will attempt to incorporate the TSD into our system shortly. A second TSD, used with the Matrox display module, will reduce display software overhead.

To facilitate preliminary evaluation of our system, software was written to enable system control from a standard terminal keyboard.

Proposed course: Due to the departure of two of the anesthesia collaborators from NIH and conflicting CSL priorities, this project will end at the close of this fiscal year. Short-term activities before project closeout will focus on the design, implementation and evaluation of display formats. In this way, we hope to be able to suggest a scheme for operating room displays that will be more efficient, informative and intelligible than those presently in use. Sample data sets will be used in these presentations. We then hope to use the TSD module to allow us to acquire, process and display realtime data.

Publication:

Lawson, D., Nadel, L., and Lees, D.: A Display Adaptor for the Vitatek #511 Monitor and the Puritan Bennett CO2 Analyzer. *Medical Instrumentation.* A.A.M.I. (in press).

Medical Information Technology Project

Principal Investigator: S. I. Allen (DCRT/CSL). *Also:* C. S. Brown (Bethesda, MD Dermatologist); R. J. Johannes (NIADDK/DDDN); J. E. Sullivan, P. S. Plexico (DCRT/CSL); A. W. Pratt (DCRT/OD).

This project involves the application of microprocessor technology and improved man-machine interface methods to permit physicians and their associates to communicate more directly with computer record systems. Pilot studies with a dermatologist for four years and a gastroenterologist for one year involve medical transactions entered directly by the practicing physicians. The goal is to develop better ways to automate the essential physician contribution to the health care record that is used in both research and patient care.

*Background and Objectives:*The use of computers in medical and hospital practice is increasing as the cost of systems is decreasing due to technological innovation. With this in mind, we are investigating devices and methods that provide a more capable, attractive interface while maintaining an acceptable level of flexibility and efficiency. The aim is to increase physician productivity in recording patient diagnoses and treatments, and to increase patient understanding of disease processes and management plans.

Progress in FY85: In collaboration with a practicing dermatologist and gastroenterologist, we are field testing and extending an ambulatory patient care transaction system. Our DEC 11/23 pilot system was converted to the IBM PC to achieve wider applicability. This system allows the physician to enter, print, and disseminate patient data needed by various members of the health care team as well as by the patient. The immediate data processing focus includes machine generation of patient information and treatment schedules, pharmacy prescriptions, and medical and surgical procedure reports.

Disease-specific and problem-specific protocols are used to lead the user through a restricted tree-structured hierarchy of relevant diagnoses, treatments, tests, and procedures. Where appropriate, protocols are modified by such factors as patient age, sex, weight, disease stage, and therapeutic response specified by physician. When all workups and treatments are indicated, the computer produces hardcopy treatment plans for the patient, record summaries for the doctor, prescriptions for the pharmacist, and test requests for specified laboratories.

Much of the clinical software is table-driven to allow the physician to update the data bases. This approach also provides a convenient means of adapting the programs to other clinical care and research environments. Sample or primer clinical data bases first are supplied by CSL staff; completed data bases are then developed by collaborating physicians in a specialty area. CSL's modular program to support these data bases, which may require some site-specific changes by CSL or others, are then installed in a compatible microcomputer system situated in the physician's office or clinic for continuing operation and refinement.

A prototype drug formulary program to safely load and update, in a step by step fashion, a rich, and sometimes complex, hierarchical drug data base was constructed for test and further development. This tool is designed to overcome the frequent errors and lack of structure that result from the standard text editor now used to add, delete, and modify prescription information files.

Work was started on a local area network to link together several workstations in an office or clinic. The

goal is to let the physician access various patient files or data bases from any workstation.

Proposed Course: Selected physician-operated modules will be enhanced to support unique diagnostic and therapeutic requirements of other ambulatory care specialties. Programming logic that now supports isolated encounters also will be expanded to handle retrieval and display key data from prior visits. Data base management functions needed to update tree-structured files such as the prescription and procedure formularies, will be improved and simplified so that users can maintain the data bases with minimum recourse to programmers or knowledge engineers. The local area network will be implemented fully in a physician's office environment.

Publications:

Brown, C.S., Allen, S. I., and Songco, D.C.: A Computerized Prescription-Writing Program for Doctors. *Methods of Information in Medicine* (in press).

Cardiac Ultrasound Image Processing

Principal Investigator: J. M. DeLeo (DCRT/CSL). *Also:* J. E. Parrillo, M. E. Parker (CC/CCM).

This project is directed towards providing the NIH Clinical Center Medical Intensive Care Unit with the ability to assess cardiac left ventricular function via computer analysis of ultrasound images of the heart.

Background and Objectives: The objective of this project is to investigate the efficiency and practicality of assessing left ventricular function from ultrasound images in the clinical setting. Ultrasound technology has advanced so that fairly sharp images are computer accessible directly in realtime; ultrasound imaging is less invasive than currently popular cineangiography and nuclear imaging methods; and advances in image processing technology and technique have provided the necessary computer hardware and software capability.

Methods Employed: Ultrasound images captured on an HP77020A Ultrasound Imaging System are transmitted directly to an HP2100 Computer System. Image processing algorithms are employed to estimate left ventricular volumes for computing ejection fractions.

Progress in FY85: Hardware difficulties encounterd in installing the ultrasound computer link and extended computer memory were overcome, but caused delay in software testing and continued development. Evaluation of various software approaches led to the conclusion that the most effective quantitative approach produces ejection fraction values from ellipsoid volume estimates, based on orthogonal area measurements. These area measurements are automatically computed by means of an adaptive gray-scale thresholding technique. Testing this technique with normal volunteers has demonstrated encouraging results. An extension cable allowing the ultrasound cart to reach patients within the Medical Intensive Care Unit has been installed so that clinical application may be demonstrated and tested at bedside.

Proposed Course: Continued testing and improvement of the methodology with normal volunteers and Intensive Care Unit patients is planned. After this, it is expected that the system will be made available to the Medical Intensive Care Unit staff for routine clinical patient care and research efforts.

Personal Computer System for Automatic Coronary Venous Flow Measurement

Principal Investigator: R. B. Dew (DCRT/CSL). *Also:* M. Leon (NHLBI).

An automated system, based on an IBM PC-XT Personal Computer, was developed to measure coronary venous blood flow during cardiac catheterization.

*Background and Objectives:*Coronary flow studies during arterial pacing are performed on patients with chest pain not explained by fixed narrowing of the coronary arteries. These studies involve measuring repeatedly great cardiac vein and coronary sinus blood flow while varying heart rate with an external cardiac pacemaker. Flow is determined by a thermodilution technique using a Baim Coronary Sinus Flow Thermal Dilution Catheter.

Formerly, technicians determined relevant temperature information for each flow measurement from waveform plots drawn by a mechanical strip-chart recorder. They

then applied mathematical formulae to determine flow. The goal of this project was to develop a computer system to automatically measure temperature change and calculate coronary venous blood flow, thereby improving the speed and accuracy with which repetitive flow determinations can be made.

*Methods Employed:*A thermodilution catheter is placed by way of the internal jugular vein into the patient's heart. The catheter's tip is equipped with two pacing electrodes for controlling heart rate, two thermistors for determining blood temperature, and a port opening to provide a means of infusing saline into the coronary venous system.

The catheter is positioned so that the proximal thermistor senses blood temperature within the coronary sinus and the distal thermistor senses blood temperature within the great cardiac vein. To measure coronary blood flow, a cold saline solution is injected at a known fixed rate from the catheter tip into the coronary sinus. The cold saline mixes with blood as the solution travels downstream past the thermistors. Because heat gained by the saline solution must equal heat lost by the blood, flow can be determined from a calculation involving the initial temperature and rate of injection of the saline solution and the change in temperature of the blood-saline mixture. This temperature change is detected by the thermistors located on the catheter wall.

The thermistors pass a varying DC voltage, proportional to temperature, through the catheter to a Baim flow analyzer that amplifies and isolates the electronic signal. The analyzer's waveform output, representing temperature, is directed to a rack monitor as well as to the computer system's analog-to-digital converter. The computer system uses digitized temperature information to determine flow, while the rack monitor provides a series of analog temperature traces for visual reference.

*Progress in FY85:*An IBM Personal Computer was equipped with a Data Translation DT-2801-A I/O Board to sample the analog output of a Baim Coronary Sinus Flow Analyzer. The system was designed to continuously process temperature data collected from the flow analyzer. Resulting coronary venous blood flow measurements are displayed on the PC's CRT screen and stored on a disk file. Hardcopy recording of case results is provided by an Epson FX-80 dot matrix printer. Program software was written in Interpreter BASIC using manufacturer supplied PCLAB machine language subroutines to control I/O functions. All system and software development was completed.

*Proposed Course:*The computer system has been installed in the Cath Lab and is used routinely to determine coronary venous blood flow. Cath Lab technicians may in the future modify the flow program to incorporate data collection from other monitoring devices, such as EKG and blood pressure transducers.

Molecular Graphics, Computer Modeling, and Sequence Analysis

Principal Investigator: B. L. Trus (DCRT/CSL). *Also:* A. C. Steven (NIADDK/LPB); P. M. Steinert (NCI/DB); B. N. Manjula (Rockefeller University); S. Havlin, G. Weiss, R. Nossal (DCRT/PSL).

The sequence of some regular proteins, together with other structural information such as data from x-ray diffraction, fiber diffraction, electron microscopy, and spectroscopic analysis, can be used to evaluate models of protein or polymer structure. Four current studies involve the sequence analysis of keratin and other intermediate filaments (with NIADDK, NCI); computer simulations of the effects of staining for helical proteins such as actin, actin with S1 subunits, and microtubules (with NIADDK); seqeuence analysis of streptococcal M5 protein (with Rockefeller Univ.); and computer models of polymers (with PSL, DCRT).

As the complete sequence of keratin, other intermediate filaments, and other helical proteins becomes available, an anaylsis of the sequence can proceed by studying periodicities in the sequence, and by computer prediction of the conformational properties of the specific amino acids in local regions of the chain. These predictions can be used to generalize structures where related sequences are available, and to draw conclusions as to similarities and differences.

Background and Objectives: It is currently possible to convincingly model and predict the structure of regular

(helical) proteins. With the current knowledge of the structure of the collagen helix, synthetic protein analogues of collagen, tropomyosin, and other regular proteins, one can extend this technology to new proteins as their sequence is experimentally determined.

Significance to Biomedical Research: Many proteins do not form three-dimensional crystalline solids whose structure can be analyzed by classical x-ray diffraction. However, if these proteins are regular, comparison and analogy with related proteins can be used to model the unknown structures in order to understand the structure and functioning of the proteins. In addition, one can use computer models to analyze possible protein structures based on criterion other than regular periodicities.

Progress in FY85: Analysis of the first complete sequence of a type II Keratin has been published. The distribution of periodicities in a biologically active Streptococcal M5 protein have been analyzed with their corresponding relation to structure. This work also has been published. Computer models have been used to study the growth of polymers and the physical properties of percolation clusters, and these results have been published. A detailed comparison of the diffraction patterns from stained and unstained helices has been published using computer simulations with defined model structures.

Methods Employed: Standard Fourier methods have been used to analyze the sequences and to cross-correlate sequences. These sequence regularities are usually correlated with structural features, such as the collagen triple helix, the alpha helix, or the tropomyosin double stranded alpha helix. Additional software has been developed at NIH to illustrate correlations and create maps of the linear sequences studied. We have developed other methods of model building to construct models of actin, actin with S1 subunits, microtubules, and simple branched polymers.

Proposed Course: As new sequences of regular (helical) proteins become available, it will be relatively easy to model these sequences and describe their structures both graphically and quantitatively.

Publications:

Havlin, S. Movshovitz, D., Trus, B., and Weiss, G. H.: Probability densities for the displacement of random walks on precolation clusters. *J. Physics A.* (in press).

Havlin, S., Nossal, R., Trus, B., and Weiss, G. H.: Diffusion on Tree-like Clusters *Phys. Rev. B* (in press).

Havlin, S., Nossal, R., Trus, B., and Weiss, G. H.: Universal substructures of percolation clusters: The skeleton. *J. Phys. A.* 17: L957-960, 1984.

Havlin, S., Trus, B., and Stanley, H. E.: Cluster-Growth Model for Branched Polymers That Are Chemically Linear. *Phys. Rev. Letters* 53: 1288-1291, 1984.

Havlin, S., Trus, B. Weiss, G. H., and Ben-Avraham, D.: The chemical distance distribution in percolation clusters. *J. Phys. A.* 18:L247-249, 1985.

Manjula, B. N., Acharya, A. S., Mische, S. M., Fairwell, T., Trus, B. L., and Fischetti, V. A.: The Complete Amino Acid Sequence of Streptococcal PEP M5 Protein. *Proceedings of the IX Lancefield International Symposium on Streptococci and Streptococcal Diseases.* Lake Yamanaka District, Japan Sept. 9-13, 1984 (in press).

Manjula, B. N., Trus, B. L., and Fischetti, V. A.: Presence of two distinct regions in the coiled-coil structure of the streptococcal Pep M5 protein: Relationship to mammalian coiled-coil proteins and implications to its biological properties. *Proc. Nat. Acad. of Sciences (USA)* 82: 1064-1068, 1985.

Steinert, P. M., Parry, D. A. D., Rocoosin, E. L., Idler, W. W., Steven, A. C., Trus, B. L., and Roop, D. R.: The Complete cDNA and Deduced Amino Acid Sequence of a Type II Mouse Epidermal Keratin of 60,000 Molecular Weight: Analysis of Sequence Differences Between Type I and Type II Keratins. *Proc. Nat. Acad. of Sciences (USA)* 81:5709-5713, 1984.

Trus, B. L., and Steven, A. C.: Comparison of Diffraction Patterns from Stained and Unstained Helices: Simulations with Defined Model Structures. *Proceedings 8th European Congress on Electron Microscopy.* Budapest, Hungary, August 13-18, 1984, pp. 1355-1356.

Trus, B. L., and Steven, A. C.: Simulations of Staining with Defined Model Structures: Comparison of Diffraction Patterns from Stained and Unstained Helices. Third Annual Symposium on Advances in Electron Microscopy Microstructure: Image Analysis, Synthesis, and Processing. Marine Biomedical Center, Duke University Marine Lab., Beaufort, N.C. September 22-23, 1984.

Virus Structure As Determined by Image Processing of Electron Micrographs

Principal Investigator: B. L. Trus (DCRT/CSL). *Also:*A. C. Steven, D. Thomas (NIADDK/LPB).

Two new virus structures have been studied using image processing techniques developed in this laboratory. The high resolution structure of the herpes simplex virus has been determined (with NIADDK and USUHS). In addition, tail fibers of bacteriophage T7 have been analyzed (with NIADDK, NCI, and Brookhaven National Laboratory). These analyses have been successful in part as a result of new software that has been developed for correlation averaging of single particles (with BEIB and NIADDK).

Background and Objectives: By studying the structure of selected viruses, we increase our understanding of

similar or related viruses. It is our primary objective to add to the pool of information, and to be able to use this information to increase our understanding about how virus structure relates to function and activity.

Significance to Biomedical Research: Viruses are significantly smaller than bacteria, and as a result are not seen in a light microscope. Information about their structure usually comes from electron microscopy, which is limited by resolution, low contrast, and noise. If staining is used, the resolution is limited by the size of the stain, and often noise as a result of uneven staining. However, because virus structures are generally periodic or contain some symmetry, they are perfect candidates for image processing. This project should be considered as basic research aimed at increasing understanding of the structure and functions of viruses in general, as well as of subclasses of viruses similar to those studied to date.

Progress in FY85: The radial reconstruction method, recently published, provides scientists with a simple real space algorithm for analysis of projection STEM data to provide radial reconstructions. The method was applied to Tobacco Mosaic Virus (TMV) as a test case, for the structure of TMV is relatively well known, and then extended to Vesicular Stomatitis Virus. A chapter on the structure of bacteriophage T7 is being published. Correlation averaging has been applied to T7 tails to study the high resolution structure, and to correlate the structure with the amino acid sequence.

Methods Employed: The micrographs were taken with a Philips EM400T microscope and the Brookhaven STEM. Some micrographs were preselected by optical diffraction. Negatives were digitized on a Perkin-Elmer 1010MG microdensitometer and analyzed by means of the PIC computer system. Results were photowritten on the Perkin-Elmer microdensitometer. Images were processed using software developed primarily at NIH.

Proposed Course: We anticipate evaluating other viruses for suitability for examination with these methods, and continuing with this ongoing project to determine the structure of various classes of viruses.

Publications:

Steven, A. C., Hainfeld, J. F., Trus, B. L., Steinert, P. M., and Wall, J. S.: Radial Distributions of Density Within Macromolecular Complexes Determined from Dark-Field Electron Micrographs. *Proc. Natl. Acad. Sci. (USA).* 81:6363-6367, 1984.

Steven, A. C., and Trus, B. L.: The Structure of Bacteriophage T7. In Harris, J. R. (Ed). *Viral Structure: Electron Microscopy of Proteins* (in press).

Thomas, D., Newcomb, W. W., Brown, J. C., Wall, J. S., Hainfeld, J. F., Trus, B. L., and Steven, A. C.: Mass and Molecular Composition of Vesicular Stomatitis Virus: a Scanning Transmission Electron Microscopy Analysis. *J. of Virology.* 54:598-607, 1985.

Thomas, D., Newcomb, W. W., Brown, J. C., Wall, J. S., Hainfeld, J. F., Trus, B. L., and Steven, A. C.: Radial Organization of the Vesicular Stomatitis Virus Determined from Dark-Field Stem Micrographs. Annual meeting of the French EM Society, Strasbourg, France, May 28-31, 1985.

Trus, B., Maizel, J. V., Studier, F. W., and Steven, A. C.: The GP17 Tail Fibers of Bacteriophage T7: Derivation of a Filamentous protein Structure from Electron Microscopy, Computer Processing, and Secondary Structure Prediction. Chesapeake Society for Electron Microscopy 1985 Annual Picture Meeting, George Washington University, May 23, 1985.

Image Processing of Electron Micrographs

Principal Investigator: B. L. Trus (DCRT/CSL). *Also:* A. C. Steven (NIADDK/LPB); P. M. Steinert (NCI/DB).

This project was designed to facilitate structure determination from electron microscopy. Suitable software, hardware, and scientific expertise has been provided to allow other scientists, primarily at NIH, to use image processing and computer reconstruction to determine or understand a specimen's structure.

Studies continued from FY84 include analysis of keratin and other intermediate filaments.

Background and Objectives: The objective of this project is to develop a general-purpose software package for the analysis of electron micrographs. In addition, the computer analysis requires optimal utilization of the available hardware and the availability of a research scientist capable of providing logistical support. Techniques and software developed in this project have been used both at NIH and at other laboratories.

Significance to Biomedical Research: Computer analysis of electron micrographs is still a relatively recent addition to the tools available to scientists for structural analysis. Few laboratories have the combined software and hardware capability to perform the image processing and image reconstruction available at NIH. These techniques are especially powerful when applied to two-dimensional crystalline structures. In addition, we can correlate and align similar particles that are not

crystalline, and correct for a number of artifacts and experimental problems.

Progress in FY85: This project has had some growth in software, but primarily has grown in the utilization of programs and the PIC system. The primary addition to software has been the ability to perform correlation averaging and correspondence analysis. It is feasible for an NIH scientist to bring in a problem and obtain preliminary results in a relatively short period of time. Then a decision is made to expand the preliminary study into a project, or to use the results obtained.

Methods Employed: The micrographs were taken with a Philips EM400T microscope and the Brookhaven STEM. Some micrographs were preselected by optical diffraction. Negatives were digitized on a Perkin-Elmer 1010MG microdensitometer and analyzed by means of the PIC computer system. Results were photowritten on the Perkin-Elmer microdensitometer. Images were processed using software developed primarily at NIH.

Proposed Course: This project will continue software development as needed. In addition, as new biological structures become available for analysis, these will be examined.

Publications:

Gershon, N. D., Naftolin, F., Sakamoto, H., Garcia-Segkura, M., and Trus, B. L.: Three-Dimensional Organization of Endoplasmic Reticulum-Like Structures in Hypothalamic Neurons. *Biophys. J.* 47:2:2, 1985.

Gershon, N. D., Porter, K. R., and Trus, B. L.: The Cytoplasmic Matrix. Its Volume, Surface Area and the Diffusion of Molecules Through It. *Proc. Natl. Acad. Sci. (USA)* (in press).

Steven, A. C., Stall, R., Steinert, P. M., and Trus, B. L.: Computational Straightening of Images of Curved Macromolecular Helices by Cubic Spline Interpolation Facilitates Structural Analysis by Fourier Methods. 1985 EMSA meeting, Louiville, Kentucky, August 5-9, 1985.

Steven, A. C., Trus, B. L., Hainfeld, J. F., Wall, J. W., and Steinert, P. M.: Conformity and Diversity in the Structures of Intermediate Filaments. *Proceedings of International Conference on Intermediate Filaments.* NY Academy of Sciences (in press).

Trachtenberg, S., Steinert, P. M., Trus, B. L., and Steven, A. C.: Paracrystalline Aggregates of Psoriatic Keratin and Their Relation to Normal Keratin Structure. 1985 EMSA Meeting, Louiville, Kentucky, August 5-9, 1985.

Trus, B. L., Pashayan, A. J., Risso, W.: Digital Image Processing of Electron Micrographs: The PIC System II. Second Annual Conference on Computers in Science: Workstations for Scientists. *Science* Magazine Conference, October 29-November 1, 1984, Washington, D.C.

Computer Analysis of Gel Electrophoresis

Principal Also: L. Leive (NIADDK/LCBG); T. Pun (DRS/BEIB).

This project was designed to allow NIH scientists to easily and accurately quantitate one- and two-dimensional gels. New software has been developed to utilize the features of the new image processing facility and more easily and quickly to analyze gels, autoradiographs, and data from hybridization experiments.

Background and Objectives: The primary objective of this project has been to develop experimental techniques and computer software to easily and automatically quantitate one- and two-dimensional gels. Initially only Coomassie blue-stained gels were analyzed, but currently, autoradiographs have been shown to be equally amenable to processing.

Significance to Biomedical Research: Use of gel electrophoresis and autoradiographs is commonplace in chemical, biochemical, and biomedical research. However, the quantitation of these gels is difficult. We have developed systems that accurately and easily provide this quantitation to the scientist.

Progress in FY85: This project has produced many useful results to a number of scientists at NIH. New methodology currently is being developed in collaboration with BEIB to automatically and quickly analyze 1-D gels. This new proceedure automatically locates lanes, subtracts background, and integrates the total content across each lane. The results are depicted graphically, and a printout is produced that includes a summary and simple plot.

Methods Employed: Wet gels are rephotographed onto Ektapan 4162 black and white film. The black and white negative (4162 or an autoradiograph) is scanned on the Perkin-Elmer 1010MG microdensitometer and stored on disk for later processing. Software to process these images was developed primarily at NIH.

Proposed Course: New software is being developed that will provide better background correction. In addition, present methods will be adapted to include hybridization experiments. Options are being added to the software to provide additional flexibility to the research scientist. A video camera is being procured to provide more rapid digitization of gels.

Publications:

Pun, T., Trus, B., Grossman, N., Leive, L., and Eden, M.: Computer Automated Computer Lanes Detection and Profiles Evaluation of One-Dimensional Gel Electrophoretic Autoradiograms. *Electrophoresis* (in press).

Cataract Quantitation Using Image Processing

Principal Investigator: B. L. Trus (DCRT/CSL). *Also:* M. Datiles, P. Edwards (NEI/CB).

Images produced by the Scheimpflug principle are being used to quantitate eye opacities in a pilot study to evalute the potential for the accurate evaluation of changes in cataract patients. This may provide a means of documenting and monitoring cataracts in vivo, allowing clinical trials of drugs that may prevent or reverse the cataract formation process.

Background and Objectives: The primary objective of this project has been to develop computer methodology to aid in the accurate interpretation reproducibility for photographs from the Topcon SL-45 camera that uses the Scheimpflug Principle to photograph lens cross-sectional areas.

Significance to Biomedical Research: Pharmaceuticals are availble that may prevent or reverse the cataract formation process. A clinical trial in human patients cannot be pursued because of inadequate means of documenting and monitoring cataracts in vivo. It is hoped that this methodology will provide the statistical and image processing foundation to document and assess changes in lens opacities in cataract patients.

Progress in FY85: This project, which began this year, is a pilot study. We are in the process of collecting data for subsequent analysis.

Methods Employed: Lens opacities are photographed on a Topcon SL-45 Scheimpflug Camera with Ektapan 35mm film. The film is digitized on a Perkin-Elmer 1010MG microdensitometer at 40 micron resolution, and analyzed by the DCRT Image Processing Facility's VAX, using Gould-DeAnza IP8500 hardware and software designed and written at NIH for this application.

Proposed Course: Once a larger data base is available, statistical analyses of the results will be needed to determine the utility and reproducibility of this approach in the assistance of cataract monitoring.

Distributed Laboratory Data Acquisition and Control System (DLDACS)

Principal Investigator: J. I. Powell (DCRT/CSL). *Also:* W. H. Jennings (NIADDK/LCP); E. R. O'Bryan, A. R. Schultz, D. C. Carpenter (DCRT/CSL); J. T. Morris (Systex, Inc.).

An integrated laboratory data acquisition and processing system has been developed for LCP and LMB, NIADDK, in NIH building 2. The system is configured with satellites coupled through a local network to a host processor. Each satellite is a dedicated microcomputer system performing data acquisition from and control over an instrument/experiment. The local network allows the host storage medium to appear as a virtual storage device to the satellites.

*Background and Objectives:*A system of microcomputers capable of independently controlling and acquiring data from an instrument/experiment was proposed in December 1976 as the best system architecture for upgrading laboratory data processing.

A Laboratory Data Acquisition and Control System (LDACS) configuration includes a Digital Equipment Corporation (DEC) LSI-11 microcomputer, 28K words memory, low density random access storage, graphics terminal, and all the necessary I/O hardware to interface the instrument/experiment. Software developed by CSL for each satellite, running under DEC's RT-11 operating system, provides the user with a turnkey system. Presently the system is configured with 10 satellites, supporting 12 instruments, connected (via the concentrator) to a DEC PDP 11/70 host processor.

Instruments connected to the network include: Spectrophotometers, Cary 118, Cary 210, Cary 219, two Perkin-Elmer 580Bs, a microspectrophotometer (designed by NIADDK); Spectropolarimeters, Jasco J500A; a Varian Electron spin resonance spectrometer; I.S. Co. Model 1440 liquid chromatograph; a SPEX spectrometer (utilizing EG&G model 1420 intensified

silicon photodiode array detector and model 1218 detector controller); a raman spectrometer (utilizing a SPEX spectrometer and compu-drive); and a stimulous response retina experiment.

The local network includes a software module, installed as a handler under the RT-11 operating system, at each satellite. Each satellite is connected via a hardwired serial link to a front-end concentrator. The concentrator performs a file store and forward function. The communications task running on the host maps the files to the appropriate directory area based on the identity of the satellite that originated the transfer and the extension of the file being transferred.

The host processor, a DEC PDP 11/70, is configured with: 640K words of memory, a high-speed printer/ plotter, an X-Y plotter, a 9-track magnetic tape drive, dual RX02 floppy disk drives, RL02 disk drive, two large capacity RA-81 Winchester disk drives, an RA-60 disk drive, a 4800 baud link to DECsystem-10 and 32 serial I/O ports. DEC's multiuser, multitasking operating system, RSX-11M PLUS, is used to service the processing needs of the users. User access to the host is provided by both hardwired links between terminals and host timesharing ports and four 300/1200 baud telephone lines.

Processing software provided at the host allows LDACS data files to be added, subtracted, averaged, smoothed, baseline corrected, integrated, differentiated, multiplied by a constant, and added to a constant. The results may be displayed graphically on a Tektronix compatible terminal, typed on a terminal, printed on a line printer, plotted on an X-Y plotter or transmitted to the NIH DECsystem-10 for additional processing.

Progress in FY 85: An LDACS unit was assembled for the Ramalog raman spectrometer. This LDACS is configured with a 30 Mbyte Winchester disk, a 10 Mbyte 'SABRE' removable cartridge disk, and a Tektronix 4105 color display terminal. The interface with the spectrometer includes direct control of the wavelength through the SPEX compu-drive unit. Acquisition of data (as pulses-per-unit time) is derived from a photon discriminator.

The retrofitting of LDACS units with the latest version of the RT-11 operating system and up-to-date software was completed. A kinetics program to record photometric data versus time for 5 samples was provided for the C118, C210, and C219 instruments. Work to utilize DAOS, an interactive data acquisition software package, on the Stimulous Response LDACS was continued and is described in a separate project report.

The RK05 disk drives on the communications processor were replaced with a Winchester disk drive. The RA-60 disk drive was delivered and installed on the 11/70 system, allowing the RP04 drives to be removed from the system.

APR, an integrated data processing and display program, was rewritten in FORTRAN-77. Software documentation was provided by internally commenting the source code, and a *USERS GUIDE* also was provided. A copy of APR source code was requested by Dr. John George, Life Sciences Division, Los Alamos National Laboratory, for use on DEC micro 11s. A version of APR (called DP2) was implemented for the Flow Cytology/Electronic Cell Sorter project (FC/ECS). DP2 has been installed at four FC/ECS sites. A version to accommodate three-dimensional display (isometric and contour) for the FC/ECS systems is under developement.

Proposed Course: Support for the system will continue, but at a reduced level. We will continue to provide maintenance support and to make minor modifications to the existing system. Major revisions or new LDACS will be treated as new projects and will depend on available resources.

Publications:

Kon, H., O'Bryan, E.R. and Kon, H.: Effect of the Presence of Hardened Erythrocytes on Deformation-Orientation Characteristics of Intact Erythrocytes in Shear Flow. *Biorheology* (in press).

Medical Image Data Compression

Principal Investigator: H. Sabrin (DCRT/CSL). *Also:* D. Syed (DCRT/CSL); B. S. Garra (CC/DR).

This project is concerned with the minimization of the number of information carrying units used to represent

a medical image in order to improve the efficiency of transmission and storage of such images. Various image data compression techniques and their application to medical images are being evaluated with regard to the amount of compression attained and the quality of the reconstructed image. Methods for implementing these techniques suitable to the clinical environment are being investigated.

Background and Objectives: Recently, there has been an increase in the number of medical imaging techniques that result in a digital image representation. These techniques include computed tomography, nuclear medicine, positron emission tomography, ultrasonography, magnetic resonance imaging, and digital radiography. As a result of this increased number of digital images, there is a need for Picture Archive and Communication Systems (PACS) that are capable of storing, transmitting, and displaying such images. Because the quantities of image data are large, it is important to consider techniques for data compression to reduce archival and transmission requirements.

Progress in FY85: During FY85, evaluation of compression techniques was continued, and implementation was begun. The work was performed on the VAX computer system at the DCRT Image Processing Facility using images obtained from the Diagnostic Radiology Department of the Clinical Center. A Hadamard transform algorithm was developed and applied to the digitized images. After considerable effort to determine the best element elimination and quantization schemes, it was found that a compression ratio of approximately 5:1 could be obtained using the Hadamard technique while maintaining acceptable image quality.

Examination of the transformed image showed that the entropy of the 8-bit values being stored ranged from 3 to 4 bits, indicating that an additional factor of 2 to 3 compression, based on an 8-bit pixel value, could be obtained without any further degradation in image quality. This compression was achieved by implementing a Huffman encoding bit-allocation scheme, and has increased the compression ratio significantly.

Significance to Biomedical Research: The results of this project will be directly applicable when a biomedical image transmission and storage system is eventually implemented within the Clinical Center. In addition, the techniques developed should benefit any medical center that needs to store and transmit a large number of medical images.

Proposed Course: With the implementation of one compression method complete, integration of this technique into a clinical setting can begin. This will be accomplished concurrently with the evaluation of reconstructed image quality obtained from the compressed transforms, and the development of other transform techniques.

Integrated Input/Output

Principal Investigator: J. S. Del Priore (DCRT/CSL).
Also: Rick Pilgrim (DCRT/DMB); David Songco (DCRT/OD); Perry Plexico (DCRT/CSL).

The Integrated Input/Output project is an attempt to expand the user interface of a personal computer from the usual keyboard input and CRT display to include more friendly and efficient modalities of communication. CSL efforts on this project include the development and modification of hardware and software to support desirable interface features like speech recognition and voice response, bar code interpretation, touch-sensitive CRT screens, and graphics input devices.

*Background and Objectives:*This project complements earlier CSL work to develop a Voice Output Terminal for blind computer users. The current trend toward widespread use of personal computers will lead to a need for many different input and output methods to suit users' requirements. The goal of the integrated input/output project is to provide user-friendly interaction in a variety of complex human-machine environments. This requires the development of tools and concepts necessary to apply personal computer technology to applications ranging from laboratory research, where the user is occupied with the manual task of operating sophisticated instrumentation, to handicapped users' environments where sight, hearing, or neuromuscular impairment must be overcome.

*Progress in FY85:*Methods were developed to let a DCRT/DMB computer programmer, who is a quadriplegic, operate and program his own personal workstation (IBM PC) by voice command. Moreover, he now can communicate through his PC to other computer facilities like the DCRT central systems.

A Multiple Input Computer Key demonstration system (MICKEY) has been developed incorporating various types of input: keyboard, touch screen, bar code, mouse, and voice recognition. This system demonstrates the flexibility and feasibility of monitoring the above inputs simultaneously, allowing for the appropriate input that suits the laboratory situation.

*Proposed Course:*We will continue to improve the voice input system for handicapped users by incorporating continuous speech recognition and investigating other voice interfaces for the handicapped. In addition, MICKEY will be expanded to include other types of inputs such as light pens, scanners, and pads.

Using the DAOS Realtime Control Language for Retina Research

Principal Investigator: R. L. Tate (DCRT/CSL). *Also:* W. A. Hagins, S. Yoshikami (NIADDK/LCP).

For many years CSL has supported retinal metabolism research in LCP, NIADDK, with computer-based systems designed primarily for high-speed data capture and processing. CSL recently selected a more flexible language system suited to this Laboratory's data acquisition needs. Especially important was the ability to support new devices as the need arose. CSL chose the Data Acquisition Operating System (DAOS), and is extending it to accommodate the special hardware and operating conditions in LCP, NIADDK.

Background and Objectives: Studies of retina electrophysiology and biochemistry often require computer-based systems designed primarily for high-speed data capture and processing.

To accommodate these requirements, CSL provided a program running on an LDACS that supervised the acquisition and display of data from a set of sources selectable with a patch panel. Although somewhat flexible, the fixed nature of the program limited the ability to adapt the data system to the frequently changing experimental protocols. Required was a more flexible language system suited to laboratory data acquisition that permitted the user to quickly adapt programs to new experimental protocols while retaining high-speed data acquisition capability. Additionaly, the ability to control the timing of events from within the program was needed.

Progress in FY85: After evaluating existing laboratory software packages, CSL selected tne Data Acquisition Operating System (DAOS), written by Laboratory Software Associates of Melbourne, Australia, as the most suitable. The major strengths of the DAOS interpreted realtime control language are support of timing functions, command macros, built-in array operators, virtual data storage, extensibility, and support for a wide variety of popular data acquisition boards.

In support of special hardware for stepping motor control and for counting and timing, CSL-designed routines have been incorporated into DAOS as extensions of the language itself. The greatest values of DAOS to the investigator lie in the rapidity with which programs may be written or changed and in its event scheduling functions. In addition, DAOS permits analysis programs already available on the Arthritis Computer Facility (ACF)to be used for analyzing data collected using DAOS.

Proposed Course: Extensions to DAOS are planned that will permit control of stepping motors used to rotate neutral density filters and drive precision fluid delivery systems. A series of command macros also are being written to simplify the process of experimental protocol setup and to make the data file format compatible with the LDACS system.

Advanced Laboratory Workstation

Principal Investigator: Keith E. Gorlen (DCRT/CSL).

The Computer Systems Laboratory is developing an Advanced Laboratory Workstation (ALW), which is a small to mid-size (K- 0K), 32-bit, UNIX-based computing engine intended for biomedical research laboratory applications. The project involves the

development and integration of a wide variety of software packages into a foundation that can be used by CSL engineers, or scientists themselves, to quickly customize an ALW for a particular purpose. We plan to include functions that are valuable in the research laboratory and that state-of-the-art technology makes economically feasible: data acquisition, scientific data processing, data presentation, networking, data base management, modeling, document preparation, and software development. Our strategy is to purchase the best software that is compatible with the workstation hardware and operating system and to integrate it under a user-friendly desktop interface. Modern programming techniques such as object-oriented programming will be explored as a means of increasing productivity and software portability.

*Background and Objectives:*Traditionally, CSL has designed its laboratory computer systems using principally DEC's PDP-11 series minicomputers and microcomputers. In its day, the PDP-11 was the logical choice for laboratory applications because of the availability of a wide variety of data acquisition and instrumentation peripherals, realtime operating systems, and scientific applications software. However, it has some serious limitations that have restricted its role in the laboratory. The foremost of these is its 65 KB address space, which necessitates using overlays for even modest-sized programs, thereby complicating implementation and maintenance. This limitation has pushed the PDP-11 out of the mainstream of software development in crucial areas such as image processing, graphics, networks, compilers, and debugging and maintenance tools in favor of the new 32-bit supermicros such as the MC68000, NS32000, and the MicroVAX.

Another important development is the emergence of UNIX as a standard operating system, and of C as a standard systems programming language. This has greatly enhanced the portability of systems-level software such as data management systems, utilities, and communications software, thereby expanding the potential user base for UNIX systems software products, thus encouraging their development and marketing. As a result, there are a large number of UNIX-compatible software packages on the market from which to choose when designing an application. Furthermore, an investment in custom software is more protected because it is not as locked-in to specific hardware.

The proposed Advanced Laboratory Workstation (ALW) will be a laboratory computing engine, suitable for the type of medium- and large-scale laboratory automation projects in which CSL has been involved. Moreover, it will address a larger range of laboratory applications such as automation of experiment design, experiment protocols, research data base maintenance, modeling, graphics, image processing, and scientific publication preparation.

*Progress in FY85:*This project was begun midyear. Most work this year consists of preliminary planning and decisionmaking. We decided to use the Tektronix 6000 series and MASSCOMP 500 series workstations for the initial implementation of the ALW. The Tektronix 6000 series uses the NS32000 series microprocessor and runs UNIX System V. It features low cost (,000-,000) and excellent graphics. The MASSCOMP 500 series uses the MC68000 series microprocessor and runs UNIX System V with Berkeley 4.2 and realtime enhancements. It features high floating-point performance and powerful realtime data acquisition and instrument control capability.

We have decided to use C as the principal implementation language for the ALW because it is widely available, reliable, portable, and useful for systems implementation. Some of C's disadvantages, such as the lack of strong type-checking and support for modular programming, we believe can be overcome by using a preprocessor to add object-oriented programming facilities. Another motivation for object-oriented programming is the complexity of the software required for the user interface that is envisioned for the ALW.

The goal is to provide software tools for implementing graphic representations of objects that the user will manipulate using the workstation's high resolution graphics display and a mouse. This technique is used by commercial products such as the Xerox Star and the Apple MacIntosh.

There are several advantages to this approach: it results in an easy-to-use system (how to do something is self-evident and easy-to-learn and remember); certain applications such as image processing require graphic input anyway; the user interface is a major component of custom applications software (providing appropriate tools will reduce design effort and encourage consistency in the user interface); and it will enable CSL's products to meet higher expectations of users who will be exposed increasingly to commercial personal computers such as the MacIntosh.

For much of the graphics software we plan to use graphics standards such as the Graphical Kernel System (GKS) and the Virtual Device Interface (VDI). However, the user interface will require facilities such as window management that are not yet standardized. Therefore, we must keep abreast of standardization efforts in these areas.

*Proposed Course:*Next year, as an experimental application of the ALW, we will replace the BEIB Electron Beam Imaging and Microspectroscopy Facility's DEC PDP 11/60 with a MASSCOMP graphics workstation. This will involve demanding realtime data acquisition, instrument control, image processing, and utilization of local area networking. Two software packages from the 11/60 will be ported to the MASSCOMP and the image display system now used on the 11/60 will be interfaced to the MASSCOMP. UNIX implementation of automatic disk backup and file archive utilities similar to those CSL developed for use on PDP-11s has already begun. We plan to implement a prototype user interface using object-oriented programming techniques to evaluate the method.

We also expect to demonstrate remote software development and support, and remote operation of the image display system via the experimental broadband link to be installed between Building 13 and the DCRT Ethernet.

We will begin evaluation, procurement, and integration of data base, spreadsheet, modeling, and text processing software.

NIH Campus Area Network

Principal Investigator: W. L. Risso (DCRT/CSL). *Also:* R. Fico (DCRT/CSL).

This project will investigate campus-wide network requirements such as the interconnection of local area networks, data commuunications among geographically separate computers, and high-speed transmission of video data.

Background and Objectives: The goal of this project is to provide NIH with an assessment of networking requirements on a campus-wide basis, to study available technology, and to recommend appropriate designs to meet the requirements. We expect to find applications ranging from video data transmission including images and graphics, to mainframe/micro computer interconnection, to interconnection among individual local area networks.

Progress in FY85 CSL began this project during this fiscal year. During the year, several potential sources of network traffic have been identified and characterized; a study of various networking technologies was begun; a contract for consultant help was initiated; and a pilot network between two adjacent buildings has been designed.

Significance to Biomedical Research: A campus-wide network would encourage the sharing and dissemination of computer data such as molecular graphics and video images from biomedical and clinical research, and would provide a mechanism for interconnection of scientific and engineering computer workstations and local area networks.

Proposed Course: Further development of a network requirements study is expected, and development of a pilot network will proceed. During FY86 CSL proposes to develop technical specifications for a campus area network, and write an RFP for competitive procurement of the hardware and software for this network.

Expert Systems in Medicine

Principal Investigator: D. Syed (DCRT/CSL). *Also:* K. M. Kempner, H. Frederickson, J. J. Knight (DCRT/CSL); J. E. Parrillo, M. A. Mazer, G. L. Akin (CC/CCM).

This project concerns the development of "expert systems" in the medical environment. Expert systems are present-day, feasible, applications of artificial intelligence techniques. They are knowledge-based, in that they contain knowledge contributed by experts, and organized, by "knowledge engineers." Generally, they function best in specific, narrowly defined, yet still complex, problem areas.

Possible medical areas for the application of expert systems include physical diagnosis, therapy planning, and clinical data interpretation. An initial objective for the project is to develop, in collaboration with the Critical Care Medicine Department of the Clinical Center, an Intravenous Chemotherapy Advisor Expert System for use in an intensive care unit.

The specific problem of interest is drug therapy to stabilize cardiodynamic function. Longer range objectives include the investigation of languages and personal computer technology for implementation of expert systems, development of techniques for this relatively new field, and application of expert systems technology to other appropriate areas such as office automation.

*Background and Objectives:*Artificial intelligence can be considered to be the state achieved when a digital computer has been programmed to perform, within a given sphere or domain, with human-like intelligence. In its simplest form, an artificial intelligence problemsolving system can be considered to contain three key elements: a knowledge base, a data base, and an inference engine.

The knowledge base contains domain knowledge in the form of facts, relationships, and rules of thumb. The data base contains data pertaining to the changing measurement space of the problem area being attacked. The inference engine controls the system's operation and essentially applies the knowledge base to the current information contained in the data base, in order to achieve the desired "intellectual" analysis. Ideally the inference engine will be domain independent and therefore applicable to any problem domain.

The real world implementation of an artificial intelligence problemsolving system is called an expert system. If properly conceived, the expert system's performance can approach the level of expertise attributed to the domain expert, whose knowledge was imparted to the expert system's knowledge base.

One of our goals is to evaluate the effectiveness and applicability of expert system techniques to dynamic medical problem areas such as the medical intensive care unit environment, in which rates of change in observed data variables, and not simply current values, are of principal importance. Additional objectives are to observe the performance in the medical domain for both data driven and goal driven expert system implementations, investigate the appropriateness of utilizing personal computing technology for building expert systems, evaluate various implementation languages (used alone and in combination), and assess the feasibility of using skeleton systems in complex medical situations.

*Methods Employed:*The initial problem area selected for study concerns the implementation of an Intravenous Chemotherapy Advisor Expert System with the goal of selecting the appropriate intravenous chemotherapy necessary to stabilize cardiodynamic function in a critically ill patient. The prototype intravenous drug administration protocol tentatively specified includes the capability for long-term dose maintenance and eventual dose tapering.

Current plans call for the initial implementation of the expert system on an IBM PC-XT personal computer utilizing one of the commercially available skeletal expert system development packages, which contain inference engines linked to empty knowledge and data bases.

Progress during FY85: The prototype intravenous drug administration protocol has been documented in flow chart format and has been translated into a general form of production rules.

A survey of artificial intelligence languages and expert systems software packages and tools was initiated and is continuing. Several skeletal expert systems development packages, which run on the IBM PC-XT, were obtained for evaluation purposes.

Significance to Biomedical Research:The successful implementation of expert systems technology in dynamic medical problem areas can be expected to pave the way for the design of more sophisticated research protocols. Expert systems will effectively allow the researcher to be continually present during the execution of protocols of long duration, and to modify, within protocol limits, the necessary medical interventions in realtime.

Proposed Course:The prototype intravenous drug administration protocol will be implemented via one or more skeletal expert system development packages. The user interface will be designed to allow the Intravenous Chemotherapy Advisor Expert System prototypes to log the physician's comments and corrections during their normal operation, in order to evaluate their long-term open-loop performance.

A short initial clinical trial period will allow a second iteration to improve the drug administration protocol, its knowledge base representation, and the system's user interface, prior to full-scale clinical trials.

Data Management Branch

J. Emmett Ward, Chief

In FY85 the Data Management Branch again worked on many projects involving virtually every major segment of NIH. These projects vary in size, complexity, and duration. The following summaries omit smaller efforts.

Clinical Research, Patient Care, Epidemiology

Bright Stat-Pack. Brian Cole (DMB/SAS); David Rodbard, Peter Munson (NICHD/BES). This computer system running on the DECsystem-10 enables CC investigators to analyze their own clinical data. During FY85 work continued on Life Table analysis, the Means program was enhanced, and a new Chi-square program was added. An interface also was designed to permit exchange of data between BRIGHT and microcomputer systems. User training and consulting continues.

Conversational Statistical Analysis System. George Roberts (DMB/SAS). The Conversational Statistical Analysis System (SAS) was developed to provide the Heart Surgery Branch (NHLBI) with a user-friendly means of statistically manipulating the voluminous data from the Heart Valve Replacement Study. As implemented, the system can be profitably utilized in a variety of areas where basic statistical analysis is needed. The CSAS provides an easy means of obtaining common statistical measures, plotting, or querying data online, by providing a preprocessor to the SAS software. By use of English style prompting, the necessity for mastering the SAS language is bypassed. The system generates and executes the required SAS code, displaying the results on the user's screen. Eleven statistical procedures, the logic/query capability of SAS, a data procedure, a print procedure, and two graphics procedures are available. This system has been used in two unrelated projects, and is being considered for a third.

Survival System. Sigurd Knisley (DMB/SAS); Ardyce Asire (NCI). This Life Table analysis system was originally developed in the 1960's to support the End Results in Cancer studies of NCI. Maintenance and improvement of the system now is the primary goal. During FY85 a copy of the system was sent to the Department of Health, Santurce, Puerto Rico.

Evaluation of Chemistry and Hematology Data for Healthy Subjects. George Shakarji, Dave Van Sant (DMB/OC); Dr. Ronald Elin (CC/CP). The serial measurements used in this study were obtained from 1200 normal participants in a program that covered a period of two and one-half years. During this period five samples of blood were collected with an interval of six months between sampling periods. Our present investigation involves 16 hematological test results for all the subjects. We are in the process of analyzing the distribution of the data for each test to a certain normality. Further analyses will involve detection and evaluation of trends, inter- and intrapersonal variation, and detection of analytical error in each of the tests.

Evaluation of Climatic Variation with Mood and Behavior. Dave Van Sant (DMB/OC); Norman Rosenthal (NIMH). This is a large ongoing study exploring the association between climate variable and mood and behavior in a population of patients who are diagnosed as suffering from seasonal affective disorder (SAD). In addition, the researchers have explored the effects of a number of interventions in this group of patients including the use of different types of artificial lighting environments and medications. The experimental interventions required extensive repeated measures analyses; then, the significant findings required multiple range tests. The findings have revealed that bright artificial light has a significant antidepressant effect on patients with SAD. Further analyses with repeated measures using day of treatment as a separate repeated measure, revealed that the antidepressant effect only becomes statistically significant by the third day of light treatment. This was a valuable statistical corroboration of a clinical impression the researchers had previously made.

IV Catheter Study. Dennis George (DMB/ASPS); John E. Bennett (NIAID/LCI). This system was developed to create a data base of catheter tip and blood culture data. This data base will be used as an aid in the reevaluation of the Clinical Center's guidelines for the use of IV catheters.

Acyclovir Treatment of Chronic EBV Infections. Dennis George, Peter Basa (DMB/ASPS); Stephen E. Straus (NIAID/LCI). This system is being developed to

establish and maintain a data base for a double-blind study of patients who are being treated with acyclovir for infectious mononucleosis.

Combined Cardiology/Heart Surgery Data System. Larry Martin (DMB/ASPS); George Roberts (DMB/SAS). This combined system provides a chronological record of the medical activity of NHLBI Cardiology and Heart Surgery Branch patients. This is an ongoing effort that supports NHLBI researchers. During FY85 a constructive analysis was undertaken of the systems capabilities and shortcomings. In lieu of a complete system redesign, an effort was made to improve data base accessibility and to standardize the production and use of SAS procedures.

Animal Heart Valve Replacement Research System. Larry Martin (DMB/ASPS); Michael Jones (NHLBI/SU). The purpose of this ongoing project is to collect, store, and retrieve information on experimental heart valves implanted in laboratory animals. Currently, the data base is being modified to include data from ultrasound studies that are performed on the animals.

Clinical Information Utility (CIU). David Blessley, William Vincent (DMB,CSS). The Clinical Support Section designed and developed two support systems this past year: 1) a system that generates a medical record using clinical laboratory, patient care, and surgical pathology data, and 2) a support system that extracts and formats special protocol data for individual research investigators. These two support systems are being run in production.

Phoenix Clinical Information System. Aileen Kelly, Ron Edwards, Nhung Pho, and David Blessley (DMB/CSS). A clinical data base management system is being developed for the Epidemiology and Field Studies Branch of NIADDK. This system, which is designed to reduce the resources needed to process the Field Studies data, is being developed and tested at the Data Management Branch. It is scheduled to be operational in the summer of 1985.

Clinical Information Utility Retrievals. David Blessley, Renee Edwards, Nhung Pho, Aileen Kelly, and William Vincent (DMB/CSS). The CIU now has over seven hundred registered users. These users, mostly research investigators, have made over five hundred requests for data during the past year.

Laboratory Investigation

Cytotoxicity Assay Program. Brian Cole (DMB/SAS); William E. Biddison (NINCDS/IRP/NIB). This is a system to analyze data from a biochemical assay using an IBM PC. A program was written in BASIC for the IBM PC to emulate an earlier program originally written for Steven Shaw (NCI) by Ramon Tate (CSL) to run on a WANG minicomputer. The IBM PC program was greatly expanded to permit accurate reading of data stored on magnetic cassette tapes from various radiation counters using MFE 5000 data loggers as input devices.

Program Management and Administration

Administrative Data Base. Data Base Applications Section (DMB); Barry Madia, Martha Alliston, Gerald Stoner (DMB/OC); Office of Administration, Office of Research Services (OD/NIH). This ongoing project utilizes data base technology in support of NIH-wide materiel and financial management activities. As the ADB entered its seventh year of development and operation, software enhancement continued to dominate work activity. During FY85 some 150 change control items successfully went into production. Of special note were the following accomplishments:

- the implementation and pilot testing of a a Market Requisition System; the implementation of a front-end ADB sign-on/menu facility coupled with an expanded security system and broadcast feature at the function level; capability to allow online source agreement searches by EIN; implementation of an online table maintenance capability whereby authorized users may change and display edit table entries, such as the purchase agent table; support of subscription processing; support of automated submittal of new EIN requests to DFM by DELPRO users; and support of intra/interagency agreements.
- the payment process in the Accounts Payable area was changed to allow final paid orders to be re-

opened for additional processing; a Cashier Tracking System was implemented to assist cashiers in buildings 10 and 31.

- the Information Center expanded the maintenance of ADB history and audit files and the production of regularly scheduled reports to include Market Requisition processing. A number of user-oriented routines allowing ad-hoc data retrieval capabilities were installed. Analysis continued of personal computer-mainframe link methodology vis-a-vis user requirements.
- the Self Service Stores S/34 computer system. The S/34 configuration was expanded for the Supply Operations Branch to accommodate the two new cashier workstations at the new self-service store in Building 10.
- the Online Market Requisition and the use of Online Vendor Request forms became operational throughout NIH.

Computer-Assisted RIF System. Brian Cole (DMB/SAS); Nelson Sparks, Lynn Hellinger (OD). In response to a mandate that all government agencies put an automated RIF system in place, Mr. Cole is developing such a system for NIH. During FY85 a prototype of the interactive system for generating RIF actions was designed and built. Programs were developed to print the master list of NIH employees by retention priority, and an online program was provided to display the retention register for any given competitive level.

Study of FY77 Subproject PIs. Dave VanSant, George Shakarji (DMB/OC); Dr. Stuart Wright (DRG). This study examined the characteristics of a nine percent sample of all subproject principal investigators active in FY77 grants, and compared them with regular principal investigators active in the same year with respect to Institute, activity, sex, and degree. As a result of the analysis, NIH decided to sponsor a second and more complete study, not only of project sub-PIs, but also of all other research professionals involved in multiproject grants. Much higher percentages of MDs and of women were found in the subproject PIs who worked primarily under multiple project grants as compared to PIs on individual, more traditional grants. Other principal findings indicated that women were, on the average, older than men. A total of 60 percent were MDs in the sub-PIs compared to 28 percent for traditional PIs; 41 percent of MDs in the sub-PIs were women, compared to 15 percent for traditional projects.

Evaluation of Personal Characteristics and Training of Grant Recipients. George Shakarji (DMB/OC); Dr. Stuart Wright (DRG). Statistical examination of personal characteristics and training continued this year for all principal investigators who were awarded their first grant in FY72 and the results were compared to their subsequent success at NIH through FY80. All descriptive data have been evaluated and multivariate analyses have been conducted on variables of training and personal characteristics with respect to measures of success. Additional appropriate variables and their weights to the final outcome have been evaluated. The final data preparation of the massive number of variables involved in the study and analysis specifications have now been completed. We now are waiting for new inquiries and specifications.

Human Nutrition Research and Information Management System. Judy Mahaffey, Dennis George (DMB/ASPS); Thomas Vogl (OD). This system was developed to provide a data base on human nutrition research and research training activities supported by the Federal Government. The system provides online query capabilities and provides reports itemizing and summarizing nutrition research activities for the fiscal year. Each participating agency assembles and submits its own data. The data is validated for accuracy and completeness as it is entered onto the data base. During the current year, full system, program, and user documentation were completed and delivered to Dr. Vogl. A series of detailed classroom instructional seminars, demonstrating the correct procedures for using the system, were given for the users from other agencies.

Interferon Production Monitoring System. Peter Basa (DMB/ASPS); Hilton Levy (NIAID/LVD). This system was developed to provide a means of monitoring the production and subsequent use of interferon on an experimental basis. The system is used to monitor, in both human and animal subjects, various production techniques and use protocols.

During the current fiscal year, SAS statistics and SAS graphics have been implemented to show the effects of drug-induced interferon productions of the body and to study body reaction to interferon injections.

Program Evaluation Information System of Grant Applicants, Trainees, and Fellows. Peter Basa (DMB/ASPS); Doris N. Wallace (DRG). This system is being developed to provide a data base on specific groups of individuals who have received NIH support through some specific mechanism or program, or about cohorts of individuals over periods of time throughout the history of NIH. The system will enable users with little computer expertise to evaluate a project or program of current interest. Also, the system should decrease the time required for experienced users of computerized data bases to obtain information from these files.

Print Shop Tracking System. Nan Miller and Nhung Pho (DMB/CSS). A system of programs was developed for NIH's Print Shop that tracks B/I/Ds print orders as they are processed through the printing system. These programs, which are run interactively, are currently being used in a test mode. They are scheduled to be put into production this fall.

Grants Management System. Renee Edwards (DMB/CSS). The systems analysis and design for a fully integrated grants management system have been completed. The final proposal was submitted to NICHD in June 1985.

Planning System (NICHD). Nan Miller (DMB/CSS). The analysis for a system that collects, stores, and retrieves data for planning purposes has been completed. The final proposal was submitted in June 1985.

Biomedical Communications Applications

Selective Dissemination of Information. Mary Lee Dante (DMB/SAS). The Scientific Applications Section has continued its support of the current awareness search requirements of NIH. A personal computer-based system from BioSciences Information Service (BIOSIS) was again offered during FY85. This service includes either hardcopy printouts of hits based on the scientists' personal interest profiles, or a floppy disk containing those hits that can be used to build a personal data base (B-I-T-S).

Computer Research and Technique Development

DCRT Local Area Network. Brian Cole (DMB/SAS); Bob Romanoff (PWO); Jim DelPriore (CSL). This effort aims to implement PCs on the Local Area Network in DCRT. DCRT is exploring the uses of network technology and microcomputer networks. Over 30 personal computers have been connected to the DCRT local area network using 3COM Ethernet equipment. DMB has performed some experiments involving downloading data from mainframe systems onto the PCs, and storing data in public volumes to be shared among PCs. Many popular applications programs, such as dBASEIII and Lotus 1-2-3, have been tested on the network. Systems for electronic mail, news, and calendar management have been evaluated. Additional software has been developed to make the network more convenient and accessible to new users. The DCRT Library has been able to distribute its new acquisitions lists over the network, and the DCRT Executive and Administrative Offices have been connected and are beginning to use the system.

RMAG Products Support. Bob Magnuson (DMB/OC). Support was provided for RMAG, SLR, Logic Subroutines, Arithmetic Subroutine, SLANG, PDOC, CP Tools, and SFOR. This support included software maintenance, customer assistance, and the teaching of formal DCRT courses.

SASM: A Structured Programming Macro Library for the IBM PC Assembler. Bob Magnuson (DMB/OC). Designed to assist IBM PC Macro Assembly Language programmers, the SASM structure macros generate block-structured programs. The generated blocks can be nested to whatever level required. A new version (2.0) was written this year.

IBM Personal Computer Support. Bob Magnuson (DMB/OC). In conjunction with DCRT's personal workstation initiative, support is provided for the introduction and use of the IBM PC. Included are

hardware component selection and testing, software creation, maintenance and evaluation, and the teaching of formal DCRT courses. Among new systems being evaluated are the two UNIX systems: XENIX and PC/IX.

Computer Center Branch

Joseph D. Naughton, Chief

Software Additions

Operating system software changes designed to improve the performance and reliability of the NIH Computer Utility required the implementation of 28 SYSGENS (software reconfigurations) during the year. Nearly 15,533 fixes, both preventive and corrective, were tested and applied to the system and 18 new releases of current software packages were installed.

C, a language developed at Bell Laboratories, became available on the NIH DECsystem-10. Initially designed as a system programming language used to write operating systems, C now is accepted widely as a general purpose language, used for many applications in numerical analysis, text processing, and data base systems. A low-level language that deals with fundamental data objects, C is popular because of its portability. C compilers are available for almost all microcomputers, 32-bit super-micros, minicomputers, and many mainframes; thus, the addition of C enhances the ability of NIH Computer Utility users to develop programs that are compatible with microcomputers and other systems.

SUPERBASIC, a new language that extends the existing BASIC language, was made available on the NIH DECsystem-10 this year. It permits variable names and descriptive labels of any length, making programming easier and allowing programs to be written in a more readable form. A major advantage of SUPERBASIC is that it compiles programs into standard DECsystem-10 BASIC, allowing the use of new features without introducing compatibility problems.

A new procedure, ADSERASE, which permits users to destroy data sets which are no longer needed, was made available this year to improve the protection of sensitive information. Normal methods for removing data from the system simply delete the index to the data and leave the data itself on the data media. Privacy regulations require that certain sensitive data be destroyed rather than simply be unavailable when no longer needed. ADSERASE permits users to destroy data sets stored on direct access devices (DASD), magnetic tape, and the Mass Storage System by overwriting the entire data set with zeros.

In conjunction with LSM, a number of software packages were updated with new releases this year. A new release of SPSS-X, the powerful statistical software system, added several helpful features, including hierarchical log-linear analysis, cluster analysis, probit and logit analysis, a general-purpose line printer plot routine, and the ability to add users' procedures to the system. A new version of REDUCE, number 3.1, was implemented on the NIH DECsystem-10, and the older version was retired. The new command-oriented system can be used interactively to carry out complicated algebraic operations.

Printers

Since its introduction, the IBM 6670 has become a popular tool for the production of scientific papers. The scope of use of the 6670 was expanded during the year and it became more versatile and reliable. The limit on the size of a data set that could be printed on the 6670 was raised to 10,000 lines, doubling the previous limit. The increase was made in response to requests from users who found the earlier restriction inconvenient. More comprehensive documents now can be produced.

The Computer Center users have adopted the 6670 to their environments and are sharing these uses with each other. VMAP, a catalogued procedure for producing manuscripts with elaborate multilined equations on the 6670, was developed and made available by the Laboratory of Statistical and Mathematical Methodology. The information EXCHANGE system also was used by 6670 users to share solution to certain situations in the alignment and/or justification of documents produced by WYLBUR.

Printing capabilities of the 3800 printers were enhanced as 38 new character sets for use on these printers were announced. The new character sets give the users a wider selection when designing output. The new sets include boldface, italic, reverse, and a more dense character set that allows more columns across a printed page.

New Terminals

A new high-speed hardcopy terminal, the M/A-COM Information Systems 5320, was offered to users of the NIH Computer Utility for use with the WYLBUR, TSO, and DECsystem-10 interactive systems. The new terminal, which replaced the T1222 terminals, offers several advantages while performing the same basic functions as the T1222.

The 5320 uses dot matrix technology to generate fast, draft-quality printing superior to that of the T1222. More versatile than the TI222, the 5320 is capable of providing double width and boldface characters and has ten programmable function keys that remain programmed after the power is turned off. Greatly reduced size and cost are the major advantages of the 5320. A two-piece table-top terminal, the 5320 can be rented either with the keyboard as a stand-alone terminal or without the keyboard to function as a printer attachment to an NIH8188 display terminal.

Training

Considerable growth occurred in the training program during the past year as the Computer Center strove to meet the diverse needs of the user community. The formal training program offered a total of 76 different courses this year, including 23 new courses in areas such as personal computers, utilities, and IBM system 370 hardware/software. A total of 2,862 requests for training were received and 2,394 students were accepted into 217 sessions of 74 different courses this year. Additional sections of popular courses were added whenever possible to meet increasing demand, while some small specialized courses were cancelled because of insufficient applications. Providing adequate formal training in a three-classroom facility continued to prove challenging; and, as in the past, the Training Unit received many more requests for classroom courses than it could accommodate. Nevertheless, 88 percent of all on-time and eligible applications were accepted. Space and scheduling problems made it impossible to meet training requests submitted after the posted deadline.

Independent training in a variety of formats continued to provide an alternative to classroom instruction. The ABC (Assisted By Computer) training system remained highly successful, enabling students to learn at their own convenience as well as at their own pace. Three new courses, Computer Literacy, Introduction to JCL, and WYLBUR Profiles, were added to the ABC program this year, joining the popular Introduction to WYLBUR course that has been available since 1983.

Computer Literacy offers a brief outline of the history of computing and explores the fundamental concepts of computing in a format designed for the beginner. Introduction to JCL covers the Job Control Language and JES2 statements needed to run batch jobs on the NIH Computer Utility. This course provides a much-needed alternative to the lecture course of the same name, which is one of the most requested and oversubscribed courses in the training curriculum. WYLBUR Profiles explains how to establish and use an individual user profile to simplify the use of WYLBUR.

More than 2500 people utilized ABC during FY85, with 519 students completing Introduction to WYLBUR, 423 completing Computer Literacy, and 259 completing Introduction to JCL.

Customer Assistance and Documentation

Frequent interaction between the user and the Computer Center is an important reason for the success of the direct user assistance provided by the Programmer Assistance and Liaison (PAL) Unit. PAL assistance insured that the resources of the utility were used in the most effective way possible, thus resolving many potential problems before they occurred. More than 23,300 customer assistance contacts were handled by Computer Center consultants, and 3705 individual Programmer Trouble Reports were researched and answered this year.

Documentation provides another means for users to make the most effective use of the NIH Computer Utility. Several WYLBUR Manuals--*Fundamentals, General Editing, Master Index, and WYLBUR Wisdom*--

were updated this year, and a revised *Terminal Operator's Guide* was published to describe the new terminals provided by the NIH Computer Center. The technical documentation service served 9,000 users and 175,090 copies of technical publications were sent to those users and to individual requesters. *The Computer Center Users Guide* was updated 8 times; 20 new technical documents were published and 40 others were revised or updated. Seven issues of *INTERFACE,* including an *Annual Index,* were published.

Office of the Director

Arnold W. Pratt, M.D., Director

Research Projects

A Computer System for Macromolecular and Cellular Graphics

Principal Investigator: Richard J. Feldmann (DCRT/OD). *Also:* B.K. Lee (DCRT/PSL); Bernard R. Brooks, Uriel Weinstein (DCRT/OD).

The molecular and cellular graphics system is a network of approximately 25 computers. The work was split into three main parts: (1) Interfacing various computers and devices at the physical, electrical, protocol, driver, application and user levels; (2) Making old programs work on the Apollo workstations that constitute the bulk of the network machines; and (3) Writing new programs for completely new machines such as the Silicon graphics workstation, the Weitek polygon processor, and the voice recognition and generation processor. Related program systems were developed for the molecular and the cellular graphics portions. A scheme for controlling the calculation, display and filming of both line drawing and surface representation types of images was developed. A variety of molecular and cellular applications were undertaken to test the capabilities of the system and improvements were made as deficiencies were found.

The Joystring Control Device

Principal Investigator: Richard J. Feldmann (DCRT/OD). *Also:*Horace E. Cascio (DRS/BEIB); Jane M. Small (DCRT/CCB); Uriel Weinstein (DCRT/OD).

The joystring is a computer-control device with computer controlled force feedback. It provides one-hand control for three dimensional objects as presented in computer graphics with true six degree of freedom input. Horace Cascio did the electronics, implementation, and debugging of the logic on the device.

The computer calculates the theoretical forces on the object as it is moved. The joystring device transmits these back to the hand of the operator. The electronics for two copies of the device were completed, the device driver for the Apollo server computer was written and simple application programs to calibrate and demonstrate the devices were written and debugged.

Improved Molecular Surface Representation Algorithm

Principal Investigator: Sigurd Knisley (DCRT/DMB). *Also:* David Cheung, Richard J. Feldmann (DCRT/OD).

The molecular surface representation algorithm that had served us for the last seven years was rewritten to provide higher spatial resolution (1024 by 1024 picture elements as compared to 512 by 512 picture elements previously) and higher color resolution (24 bits of color information yielding 16 million color combinations as compared to 8 bits of color information yielding 256 color combinations previously).

The resulting algorithm produces pictures of molecules that at times cannot be distinguished from photographs of plastic models. The algorithm has been in use for the last nine months and tens of thousands of pictures and several movies have already been produced by it. The program, written in PASCAL, is being used in several other institutions.

Implementation of CHARMM on the molecular and cellular graphics system

Principal Investigator: Bernard R. Brooks (DCRT/OD). *Also:* Richard J. Feldmann (DCRT/OD).

CHARMM (Chemistry at HARvard Molecular Mechanics) is the program system for molecular energy calculations developed at the Department of Chemistry of Harvard University by Professor Martin Karplus, Dr. Bernard Books, and coworkers.

The programs have been implemented at DCRT on the Apollo network and have been tested using standard test cases. Several small problems from Institute scientists have been studied using CHARMM in order to determine what features must be modified and added to suit the needs of the NIH environment. Several long-term projects have been initiated. Planning was done for the implementation of portions of CHARMM in the Star Technologies array processor.

Personal Computer Implementation on Local Area Networks

Principal Investigator: Robert J. Romanoff (DCRT/PWO). *Also:* James S. Del Priore (DCRT/CSL); Brian R. Cole (DCRT/DMB).

This is a collaborative project between PWO, DMB, and CSL to: investigate local area network (LAN) technology as it relates to personal computers (PCs), implement PCs on the DCRT Ethernet LAN, and share the knowledge developed with other NIH organizations.

Background and Objectives: The DCRT Ethernet LAN was installed in early FY85 as the first step in developing expertise in LAN technology. The LAN interconnects a great variety of computer systems in use throughout DCRT. This particular project was established to develop and implement a plan for the connection and use of PCs on the DCRT Ethernet and to investigate LAN technology as it applies to PCs in the NIH environment. The knowledge and experience gained will form the basis of advice given to other NIH organizations.

Progress in FY85: A master plan was developed and its implementation begun. Three IBM PC-XTs were installed as dedicated network servers using 3COM Corporation Etherseries hardware and software. The software allows data volume and printer sharing as well as providing an extensive interuser mail facility. The servers are located in the Personal Workstation Office (PWO), Computer Systems Laboratory (CSL), and the Data Management Branch (DMB), DCRT. Approximately 20 PC users were initially attached to the network. After replacement of the PWO and CSL servers with higher capacity state-of-the-art computers designed specifically to be servers, the number of users defined to the network grew to approximately 70. The new servers also have tape backup facilities that allow automatic backup of data on any of the network servers.

The need for a user-friendly software interface to the network commands was recognized early. To meet this need, the DOWARE software system was developed and implemented by James Del Priore of CSL. DOWARE also allows new network functions, such as newsboards, software demonstration facilities, and user memo pads to be added and gives options to the network server administrators for controlling access to the network commands.

The testing of network-oriented applications was started by various DCRT Labs/Branches. The DCRT Library began testing an online acquisition list and the use of electronic mail for communicating with DCRT employees on library issues. The development of an online search system for cataloged library items also is being developed. The DMB has actively and extensively tested the 3COM Etherseries software via DOWARE. The DMB also tested many PWO-supported software products in a network environment.

Many sessions were held to familiarize other NIH organizations with our experiences, to discuss their needs for networking and to demonstrate existing capabilities.

To help keep abreast of other current LAN technology, a five-station version of the new IBM PC Network was purchased for familiarization. This network represents a different approach to LANs than the existing network. The IBM PC Network uses broadband rather than baseband technology and allows information and resources to be shared on a PC-to-PC bases rather than through an intermediate computer. Members of this project are coordinating efforts by CSL and DMB to test the IBM network and report experiences.

Future Plans: The master plan will be revised periodically to reflect our experiences and the rapidly advancing state of LAN technology. Plans to add more functionality to DOWARE are being formulated by members of the project. Several administrative office procedures will be developed for the PC and LAN environment. Other applications such as an online calendaring system also will be developed.

A new generation of software for our existing LAN is expected to be available early in FY86. This software will allow many more commercially available applications to be used in a multi-user environment. This software, when combined with new hardware, also will allow different independent networks to communicate with each other. We plan to install another LAN similar to the existing one for the DCRT employees in building 31 with capacity for the two

LANs to access each other. We also plan to modify our capabilities to take advantage of the new functions available.

Comprehensive user and network server administrator manuals are expected to be completed in FY86 to replace the initial versions that are now available.

Consulting with other NIH organizations is expected to continue.

English Text Processing Systems

Principal Investigator: Paul J. Kalkowski (DCRT/OD).

The purpose of this project is to provide computer systems for the processing of English text. Two programs are now available: an English Reader Program, which reads English text, parses sentences, and creates an index; and an English Retrieval Program, which retrieves English text.

Background: Parsing English text by computer presents many problems. One major problem is that natural language is too ambiguous, and computer programs will in general produce not just one parse for a sentence, but many parses. A second major problem is that the human mind, in understanding or generating language, brings to bear much knowledge that a computer does not have, or that is at present difficult to obtain and represent in a computer.

The English Reader Program, previously developed, refers to an auxiliary dictionary for knowledge that its parsing algorithm lacks. The auxiliary dictionary contains the technical vocabulary used in a particular field of knowledge and enables the program to enter terms in its output index that it would otherwise be unable to find.

Work done in FY85: The ability to define relations among terms in the Reader Program's auxiliary dictionary has been extended in order to provide greater control over the content of the output index: hierarchical terms can be defined so that a given term can be indexed within the entry for a higher-level term; synonyms can be defined so that references to a preferred term are placed in the index with the entries for secondary terms; substitute terms can be defined so that a term found in text can be transformed before it is entered in the index; and generator terms can be defined so that a term found in text can produce multiple index entries.

A Retrieval Program has been written that can use an index such as that created by the Reader Program to retrieve text. A retrieval request may consist of a word, a term, a truncated word or term, or an expression composed of terms connected by Boolean operators (and, or, not). The Retrieval Program may be executed either in the batch or timesharing mode. The time for retrievals is minimal because both the data set of English text and the index data set are organized for random access; and the index data set provides the exact locations where terms can be found in text, without the necessity of sequentially searching either index or text.

Electronic Typesetting Methods

Principal Investigator: Patricia O. Miller (DCRT/OD). *Also:* Sid Nichols, Harry Phelps (GPO).

This project, begun in FY81, involves collecting and encoding text on magnetic tape for typesetting by GPO. Eliminating rekeying by a typesetter, and thus the galley proof stage of production, has cut typesetting costs 80 percent.

This year, we began research using the IBM PC as an input device to create computer processable files compatible with GPO's Automated Composition System.

Future plans include investigation of affordable desktop publishing systems suitable for a government printing environment that would enable us to transform text processed on the IBM PC into professional-quality typeset pages.

Computerized Typesetting Consultation

Principal Investigator: Patricia O. Miller. *Also:* Ed Driscoll, Betty MacVicar (NIH/OD); Brent Jacquet, Anne Atlee (NIDR).

DCRT techniques for using WYLBUR to prepare text for direct input to computerized typesetting systems have been made available to others in the NIH public affairs community.

This year, consultations with B/I/Ds included: Editorial Operations Branch, OD/NIH (GPO design sessions, coding assistance, computer account advice for the NIH Scientific Directory/Bibliography) and NIDR (for its annual report).

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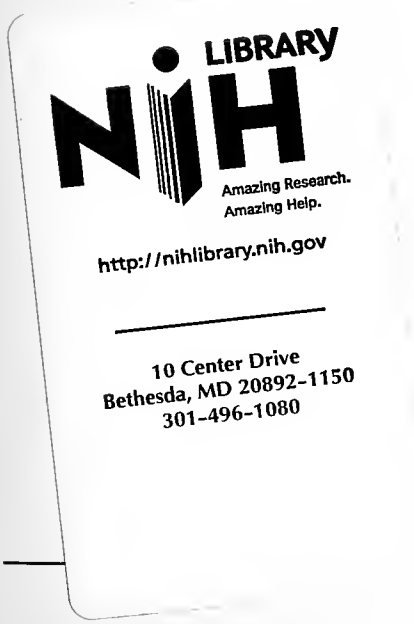

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